



DIGITAL ACCESS TO SCHOLARSHIP AT HARVARD

Novel Loci for Adiponectin Levels and Their Influence on Type 2 Diabetes and Metabolic Traits: A Multi-Ethnic Meta-Analysis of 45,891 Individuals

The Harvard community has made this article openly available.
[Please share](#) how this access benefits you. Your story matters.

Citation	Dastani, Zari, Marie-France Hivert, Nicholas Timpson, John R. B. Perry, Xin Yuan, Robert A. Scott, Peter Henneman, et al. 2012. Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: A multi-ethnic meta-analysis of 45,891 individuals. PLoS Genetics 8(3): e1002607.
Published Version	doi:10.1371/journal.pgen.1002607
Accessed	February 19, 2015 10:30:55 AM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:9795665
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)

Novel Loci for Adiponectin Levels and Their Influence on Type 2 Diabetes and Metabolic Traits: A Multi-Ethnic Meta-Analysis of 45,891 Individuals

Zari Dastani^{1,9}, Marie-France Hivert^{2,3,9}, Nicholas Timpson^{4,9}, John R. B. Perry^{5,6,9}, Xin Yuan^{7,9}, Robert A. Scott^{8,9}, Peter Henneman^{9,9}, Iris M. Heid^{10,9}, Jorge R. Kizer^{11,9}, Leo-Pekka Lyytikäinen^{12,9}, Christian Fuchsberger^{13,9}, Toshiko Tanaka¹⁴, Andrew P. Morris⁵, Kerrin Small^{15,16}, Aaron Isaacs^{17,18}, Marian Beekman¹⁹, Stefan Coassin²⁰, Kurt Lohman²¹, Lu Qi²², Stavroula Kanoni¹⁶, James S. Pankow²³, Hae-Won Uh²⁴, Ying Wu²⁵, Aurelian Bidulescu²⁶, Laura J. Rasmussen-Torvik²⁷, Celia M. T. Greenwood²⁸, Martin Ladouceur²⁹, Jonna Grimsby^{3,30}, Alisa K. Manning³¹, Ching-Ti Liu³¹, Jaspal Kooner³², Vincent E. Mooser⁷, Peter Vollenweider³³, Karen A. Kapur³⁴, John Chambers³⁵, Nicholas J. Wareham⁸, Claudia Langenberg⁸, Rune Frants⁹, Ko Willems-vanDijk⁹, Ben A. Oostra^{18,36}, Sara M. Willems¹⁷, Claudia Lamina²⁰, Thomas W. Winkler¹⁰, Bruce M. Psaty^{37,38}, Russell P. Tracy³⁹, Jennifer Brody⁴⁰, Ida Chen⁴¹, Jorma Viikari⁴², Mika Kähönen⁴³, Peter P. Pramstaller^{44,45,46}, David M. Evans⁴, Beate St. Pourcain⁴⁷, Naveed Sattar⁴⁸, Andrew R. Wood⁶, Stefania Bandinelli⁴⁹, Olga D. Carlson⁵⁰, Josephine M. Egan⁵⁰, Stefan Böhringer²⁴, Diana van Heemst⁵¹, Lyudmyla Kedenko⁵², Kati Kristiansson⁵³, Marja-Liisa Nuotio⁵³, Britt-Marie Loo⁵⁴, Tamara Harris⁵⁵, Melissa Garcia⁵⁵, Alka Kanaya⁵⁶, Margot Haun²⁰, Norman Klopp⁵⁷, H.-Erich Wichmann^{57,58,59}, Panos Deloukas¹⁶, Efi Katsareli⁶⁰, David J. Couper⁶¹, Bruce B. Duncan^{62,63}, Margreet Kloppenburg⁶⁴, Linda S. Adair⁶⁵, Judith B. Borja⁶⁶, DIAGRAM+ Consortium[‡], MAGIC Consortium[‡], GLGC Investigators[‡], MuTHER Consortium, James G. Wilson⁶⁷, Solomon Musani⁶⁸, Xiuqing Guo⁶⁹, Toby Johnson^{34,70,71}, Robert Semple⁷², Tanya M. Teslovich¹³, Matthew A. Allison⁷³, Susan Redline⁷⁴, Sarah G. Buxbaum⁷⁵, Karen L. Mohlke²⁵, Ingrid Meulenbelt¹⁹, Christie M. Ballantyne⁷⁶, George V. Dedoussis⁶⁰, Frank B. Hu²², Yongmei Liu²¹, Bernhard Paulweber⁵², Timothy D. Spector¹⁵, P. Eline Slagboom⁷⁷, Luigi Ferrucci¹⁴, Antti Jula⁵⁴, Markus Perola⁵³, Olli Raitakari⁷⁸, Jose C. Florez^{30,79,80,81}, Veikko Salomaa⁸², Johan G. Eriksson^{83,84,85,86,87}, Timothy M. Frayling⁶, Andrew A. Hicks⁴⁴, Terho Lehtimäki¹², George Davey Smith⁴, David S. Siscovick⁸⁸, Florian Kronenberg²⁰, Cornelia van Duijn^{17,18}, Ruth J. F. Loos⁸, Dawn M. Waterworth⁷, James B. Meigs^{3,30}, Josee Dupuis^{31,89}, J. Brent Richards^{15,90}*

1 Department of Epidemiology, Biostatistics, and Occupational Health, Jewish General Hospital, Lady Davis Institute, McGill University, Montreal, Canada, **2** Department of Medicine, Université de Sherbrooke, Sherbrooke, Canada, **3** General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **4** MRC CAfE Centre and School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom, **5** Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom, **6** Genetics of Complex Traits, Peninsula Medical School, University of Exeter, Exeter, United Kingdom, **7** Genetics, GlaxoSmithKline, King of Prussia, Pennsylvania, United States of America, **8** MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, United Kingdom, **9** Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands, **10** Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Regensburg, Germany, **11** Departments of Medicine and Public Health, Weill Cornell Medical College, New York, New York, United States of America, **12** Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, Tampere, Finland, **13** Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, United States of America, **14** Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, United States of America, **15** Department of Twin Research and Genetic Epidemiology, King's College London, London, United Kingdom, **16** Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom, **17** Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands, **18** Centre for Medical Systems Biology, Leiden, The Netherlands, **19** Section of Molecular Epidemiology, Leiden University Medical Center and The Netherlands Genomics Initiative, The Netherlands Consortium for Healthy Aging, Leiden, The Netherlands, **20** Division of Genetic Epidemiology, Innsbruck Medical University, Innsbruck, Austria, **21** Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States of America, **22** Harvard School of Public Health, Boston, Massachusetts, United States of America, **23** Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, United States of America, **24** Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands, **25** Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, United States of America, **26** Cardiovascular Research Institute, Morehouse School of Medicine, Atlanta, Georgia, United States of America, **27** Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States of America, **28** Lady Davis Institute for Medical Research, Department of Oncology, McGill University, Montreal, Canada, **29** Department of Human Genetics McGill University, Montreal, Canada, **30** Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States of America, **31** Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United States of America, **32** Cardiology, Ealing Hospital National Health Service (NHS) Trust, London, United Kingdom, **33** Department of Internal Medicine, University of Lausanne, Lausanne, Switzerland, **34** Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland, **35** Epidemiology and Biostatistics, Imperial College London, London, United Kingdom, **36** Department of Clinical Genetics and Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands, **37** Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of

Washington, Seattle, Washington, United States of America, **38** Group Health Research Institute, Group Health Cooperative, Seattle, Washington, United States of America, **39** Departments of Pathology and Biochemistry, University of Vermont, Burlington, Vermont, United States of America, **40** Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, United States of America, **41** Medical Genetics Research Institute, Cedars Sinai Medical Center, Los Angeles, California, United States of America, **42** Department of Medicine, University of Turku and Turku University Hospital, Turku, Finland, **43** Department of Clinical Physiology, University of Tampere and Tampere University Hospital, Tampere, Finland, **44** Center for Biomedicine, European Academy Bozen/Bolzano (EURAC) (Affiliated Institute of the University of Lübeck, Lübeck, Germany), Bolzano, Italy, **45** Department of Neurology, General Central Hospital, Bolzano, Italy, **46** Department of Neurology, University of Lübeck, Lübeck, Germany, **47** School of Social and community medicine, University of Bristol, Bristol, United Kingdom, **48** British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom, **49** Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy, **50** Laboratory of Clinical Investigation, National Institute of Aging, Baltimore, Maryland, United States of America, **51** Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands, **52** First Department of Internal Medicine, St. Johann Spital, Paracelsus Private Medical University Salzburg, Salzburg, Austria, **53** Public Health Genomics Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, and Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland, **54** Population Studies Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Turku, Finland, **55** Intramural Research Program, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, United States of America, **56** Division of General Internal Medicine, Women's Health Clinical Research Center, University of California San Francisco, San Francisco, California, United States of America, **57** Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany, **58** Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany, **59** Klinikum Großhadern, Munich, Germany, **60** Harokopio University, Athens, Greece, **61** Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America, **62** School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, **63** Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America, **64** Department of Rheumatology and Department of Clinical Epidemiology, Leiden, The Netherlands, **65** Department of Nutrition, University of North Carolina, Chapel Hill, North Carolina, United States of America, **66** Office of Population Studies Foundation, University of San Carlos, Cebu City, Philippines, **67** Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi, United States of America, **68** Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, United States of America, **69** Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, United States of America, **70** University Institute of Social and Preventative Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland, **71** Swiss Institute of Bioinformatics, Lausanne, Switzerland, **72** Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom, **73** Department of Family and Preventive Medicine, University of California San Diego, La Jolla, California, United States of America, **74** Brigham and Women's Hospital, Boston, Massachusetts, United States of America, **75** Jackson Heart Study Coordinating Center, Jackson State University, Jackson, Mississippi, United States of America, **76** Baylor College of Medicine and Methodist DeBakey Heart and Vascular Center, Houston, Texas, United States of America, **77** Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, **78** Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and the Department of Clinical Physiology, Turku University Hospital, Turku, Finland, **79** Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, United States of America, **80** Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **81** Diabetes Research Center, Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **82** Chronic Disease Epidemiology and Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland, **83** Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland, **84** Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland, **85** Folkhalsan Research Centre, Helsinki, Finland, **86** Vaasa Central Hospital, Vaasa, Finland, **87** Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland, **88** University of Washington, Seattle, Washington, United States of America, **89** National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, United States of America, **90** Departments of Medicine, Human Genetics, Epidemiology, and Biostatistics, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, Canada

Abstract

Circulating levels of adiponectin, a hormone produced predominantly by adipocytes, are highly heritable and are inversely associated with type 2 diabetes mellitus (T2D) and other metabolic traits. We conducted a meta-analysis of genome-wide association studies in 39,883 individuals of European ancestry to identify genes associated with metabolic disease. We identified 8 novel loci associated with adiponectin levels and confirmed 2 previously reported loci ($P=4.5 \times 10^{-8}$ – 1.2×10^{-43}). Using a novel method to combine data across ethnicities ($N=4,232$ African Americans, $N=1,776$ Asians, and $N=29,347$ Europeans), we identified two additional novel loci. Expression analyses of 436 human adipocyte samples revealed that mRNA levels of 18 genes at candidate regions were associated with adiponectin concentrations after accounting for multiple testing ($p < 3 \times 10^{-4}$). We next developed a multi-SNP genotypic risk score to test the association of adiponectin decreasing risk alleles on metabolic traits and diseases using consortia-level meta-analytic data. This risk score was associated with increased risk of T2D ($p=4.3 \times 10^{-3}$, $n=22,044$), increased triglycerides ($p=2.6 \times 10^{-14}$, $n=93,440$), increased waist-to-hip ratio ($p=1.8 \times 10^{-5}$, $n=77,167$), increased glucose two hours post oral glucose tolerance testing ($p=4.4 \times 10^{-3}$, $n=15,234$), increased fasting insulin ($p=0.015$, $n=48,238$), but with lower in HDL-cholesterol concentrations ($p=4.5 \times 10^{-13}$, $n=96,748$) and decreased BMI ($p=1.4 \times 10^{-4}$, $n=121,335$). These findings identify novel genetic determinants of adiponectin levels, which, taken together, influence risk of T2D and markers of insulin resistance.

Citation: Dastani Z, Hivert M-F, Timpson N, Perry JRB, Yuan X, et al. (2012) Novel Loci for Adiponectin Levels and Their Influence on Type 2 Diabetes and Metabolic Traits: A Multi-Ethnic Meta-Analysis of 45,891 Individuals. *PLoS Genet* 8(3): e1002607. doi:10.1371/journal.pgen.1002607

Editor: Peter M. Visscher, The University of Queensland, Australia

Received: September 30, 2011; **Accepted:** February 3, 2012; **Published:** March 29, 2012

Copyright: © 2012 Dastani et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: Baltimore Longitudinal Study of Aging (BLSA): The BLSA was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. A portion of that support was through an R&D contract with MedStar Research Institute. Erasmus Rucphen Family (ERF). The ERF study was supported by grants from The Netherlands Organisation for Scientific Research, Erasmus MC and the Centre for Medical Systems Biology (CMSB), and the European Network for Genetic and Genomic Epidemiology (ENGAGE) consortium. Invecchiaire in Chianti (InCHIANTI). JRB Perry is a Sir Henry Wellcome Postdoctoral Research Fellow (092447/Z/10/Z). Framingham Heart Study (FHS): This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. The Collaborative Health Research in the Region of Augsburg (KORA F3): This study was partially funded by the "Tiroler Wissenschaftsfonds" (Project UNI-0407/29) and by the "Genomics of Lipid-associated Disorders – GOLD" of the "Austrian Genome Research Programme GEN-AU" to F Kronenberg. The MONICA/KORA Augsburg cohort study was financed by the Helmholtz Zentrum München. It was further funded by the NIH subcontract from the Children's Hospital, Boston, US, (H-E Wichmann and IM Heid, prime grant 1 R01 DK075787-01A1 to JN Hirschhorn) and the German National Genome Research Net NGFN2 and NGFNplus (H-E Wichmann 01GS0823). TwinsUK: Study was funded by the Wellcome Trust, European Commission Framework (FP7/2007–2013), ENGAGE project HEALTH-F4-2007-201413, and the FPS GenomEUtwin Project (QLG2-CT-2002-01254). It also receives support from the Arthritis Research Campaign, Chronic Disease Research Foundation, the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London, and a Biotechnology and Biological Sciences Research Council project grant (G20234). Cardiovascular Health Study (CHS): The CHS research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, N01-HC-45133, grant numbers U01 HL080295 and R01 HL087652, HL105756, and HL094555 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/pi.htm>. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01-RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center, NHLBI R01-HL085251. Helsinki Birth Cohort Study (HBCS): HBCS has been supported by grants from Academy of Finland (project numbers 114382, 126775, 127437, 129255, 129306, 130326, 209072, 210595, 213225, 216374), Finnish Diabetes Research Society, Finnish Foundation for Pediatric Research, Samfundet Folkhälsan, Juho Vainio Foundation, Novo Nordisk Foundation, Finska Läkaresällskapet, Päivikki and Sakari Sohlberg Foundation, Signe and Ane Gyllenberg Foundation, and Yrjö Jahnsson Foundation. DILGOM survey was funded by the Finnish Academy, grant number 118065. Cardiovascular Risk in Young Finns (YFS): The Young Finns Study has been financially supported by the Academy of Finland: grants 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi), the Social Insurance Institution of Finland, Kuopio, Tampere and Turku University Hospital Medical Funds, Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research (T.L., OT.R), Tampere Tuberculosis Foundation (Te.Le., Mik, Kä), the Emil Aaltonen Foundation (T.L.) and Finnish Cultural Foundation. The expert technical assistance in the statistical analyses by Irina Lisinen and Ville Aalto are gratefully acknowledged. Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM): K Kristiansson was supported by the Orion-Farmos Research Foundation and the Academy of Finland (grant no. 125973). M Perola and V Salomaa were supported by the Finnish Foundation for Cardiovascular Research, the Sigrid Jusélius Foundation, and the Academy of Finland (grants 129322, 129494 and 139635). JG Eriksson was supported by the Academy of Finland (grants 126775, 129255, 129907, and 135072). Fenland study: The Fenland Study is funded by the Wellcome Trust and the Medical Research Council, as well as by the Support for Science Funding programme and CamStrad. We are grateful to all the volunteers for their time and help, and to the General Practitioners and practice staff for help with recruitment. We thank the Fenland Study co-ordination team and the Field Epidemiology team of the MRC Epidemiology Unit for recruitment and clinical testing. Multiethnic Study of Atherosclerosis (MESA): The MESA project is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, and RR-024156. Funding for CaRe genotyping was provided by NHLBI Contract N01-HC-65226. Jackson Heart Study (JHS): The Jackson Heart Study is supported by the National Heart, Lung, and Blood Institute, through contracts with Jackson State University (N01-HC-95170), the University of Mississippi Medical Center (N01-HC-95171), and Tougaloo College (N01-HC-95172). Adiponectin measurements used in the current study were funded by PHS Award UL1 RR025008 from the Clinical and Translational Science Award program, National Institutes of Health, National Center for Research Resources (NCRR). Health ABC: This research was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. Genetics, Arthritis, and Progression) study (GARP): This study was supported the Leiden University Medical Centre and the Dutch Arthritis Association. Pfizer, Groton, CT, USA supported the inclusion of the GARP study. The genotypic work was supported by the Netherlands Organization of Scientific Research (MW 904-61-095, 911-03-016, 917 66344 and 911-03-012), Leiden University Medical Centre and the Centre of Medical System Biology and Netherlands Consortium for Healthy Aging both in the framework of the Netherlands Genomics Initiative (NGI). The adiponectin measurements were supported by TI-Pharma. Atherosclerosis Risk in Communities (ARIC): The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367, R01HL086694, and RC2 HL102419; National Human Genome Research Institute contract U01HG004402; National Institutes of Health contract HHSN268200625226C; and National Institute of Diabetes and Digestive and Kidney Diseases R01DK056918. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. Salzburg Atherosclerosis Prevention Program in subjects at High Individual Risk (SHAPIR): Part of this work was funded by the "Genomics of Lipid-associated Disorders" (GOLD) of the "Austrian Genome Research Programme" (GEN-AU) to Florian Kronenberg, and grants from the "Medizinische Forschungsgesellschaft Salzburg" and the "Kamillo Eisner Stiftung" (Switzerland) to Bernhard Paulweber. THISEAS: The genotyping of the THISEAS study was funded by the Wellcome Trust. The recruitment was partially supported by the General Secretary of Research and Technology (PENED 03<EPSILON><DELTA>474). We are grateful to all the volunteers for their time and help, the medical staff of the hospitals and the field investigators, Eirini Theodoraki, Maria Dimitriou and Kathy Stirrups for her assistance in the genotyping. Cebu Longitudinal Health and Nutrition Survey (CLHNS): We thank the Office of Population Studies Foundation research and data collection teams and the study participants who generously provided their time for this study. This work was supported by National Institutes of Health grants DK078150, TW05596, HL085144, RR20649, ES10126, and DK56350. Coordinating Centre: McGill University. This work was supported by grants from the Canadian Foundation for Innovation, the Canadian Institutes of Health Research (CIHR), Fonds de la recherche en santé du Québec, the Lady Davis Institute, the Ministère du Développement économique, de l'Innovation et de l'Exportation du Québec and the Jewish General Hospital. JB Richards and Z Dastani are supported by the CIHR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: DM Waterworth, X Yuan, and VE Mooser are full-time employees of GlaxoSmithKline. P Vollenweider received grant money from GlaxoSmithKline to fund the CoLaus study. The other authors declare no competing financial interests.

* E-mail: brent.richards@mcgill.ca

☛ These authors contributed equally to this work.

☛ These authors also contributed equally to this work.

‡ Memberships of these consortia are provided in the Acknowledgments.

Introduction

Adiponectin is a highly abundant adipocyte-derived plasma protein whose levels correlate inversely with a range of important

clinical parameters including blood glucose, indices of insulin resistance, proatherogenic dyslipidemia, and risk of type 2 diabetes (T2D), stroke and coronary artery disease [1,2,3,4]. Collectively these conditions account for most of the burgeoning pandemic of

Author Summary

Serum adiponectin levels are highly heritable and are inversely correlated with the risk of type 2 diabetes (T2D), coronary artery disease, stroke, and several metabolic traits. To identify common genetic variants associated with adiponectin levels and risk of T2D and metabolic traits, we conducted a meta-analysis of genome-wide association studies of 45,891 multi-ethnic individuals. In addition to confirming that variants at the *ADIPOQ* and *CDH13* loci influence adiponectin levels, our analyses revealed that 10 new loci also affecting circulating adiponectin levels. We demonstrated that expression levels of several genes in these candidate regions are associated with serum adiponectin levels. Using a powerful novel method to assess the contribution of the identified variants with other traits using summary-level results from large-scale GWAS consortia, we provide evidence that the risk alleles for adiponectin are associated with deleterious changes in T2D risk and metabolic syndrome traits (triglycerides, HDL, post-prandial glucose, insulin, and waist-to-hip ratio), demonstrating that the identified loci, taken together, impact upon metabolic disease.

obesity-related morbidity and mortality that poses a severe and global healthcare challenge [5]. Murine studies suggest that adiponectin plays a mediating role in at least some of these obesity-related complications, and although less clearly established in humans, this suggests that understanding the pathophysiology of adiponectin may uncover novel therapeutic targets in major, highly prevalent human disease. [6,7].

Twins and family studies have revealed moderate to high estimates of heritability (30–70%) for plasma adiponectin levels [8,9,10,11]. However, until recently, few genes associated with adiponectin levels have been identified. Candidate and genome-wide association studies (GWAS) have shown pronounced associations between common polymorphisms in the adiponectin gene (*ADIPOQ*) and adiponectin levels [12,13,14,15]. A recent meta-analysis of three GWAS for adiponectin levels identified variants in a novel candidate gene, *ARL15*, that were associated with adiponectin levels, coronary heart disease (CHD), T2D and other metabolic traits [16]. Furthermore, *CDH13* and *KNG1* genes were found to be associated with adiponectin levels in two studies involving East Asian populations [17,18]. Although part of the variance explained by the *ADIPOQ* locus, most of the heritability of adiponectin levels remains unaccounted for. Therefore, we sought to identify novel common variants influencing adiponectin levels and test their association with risk of T2D and related metabolic traits within the framework of a large multi-ethnic consortium of GWAS.

We combined genome-wide association results of 35,355 individuals from three different ethnicities (white Europeans ($n = 29,347$), African American ($n = 4,232$) and East Asians ($n = 1,776$)), applying a novel meta-analytic method to allow for heterogeneity in allelic effects between populations of different ethnic backgrounds. We next examined whether identified genome-wide significant single nucleotide polymorphisms (SNPs) also associated with expression of their nearest gene in human adipocytes, the main source of adiponectin. Since adiponectin has been associated with T2D, insulin resistance and metabolic traits we next investigated whether a multi-SNP genotypic risk, comprising genome-wide significant SNPs for adiponectin levels, also influenced risk of T2D and related traits measured in the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM+)

[19], Meta-Analysis of Glucose and Insulin Related Traits Consortium (MAGIC) [20], Genetic Investigation of ANthropometric measures Traits (GIANT) [21], Global Lipids Genetic Consortium (GLGC) [22], and Body Fat GWAS consortia [23].

Results

Results of Meta-Analysis of GWAS

The meta-analysis was divided into four phases 1) Discovery phase, which involved cohorts providing GWAS results, 2) In-silico replication phase which included additional GWAS cohorts joining our meta-analysis after the completion of the discovery phase, 3) De-novo genotyping in cohorts without GWAS genotyping and 4) Multi-Ethnic meta-analysis applying a novel method for complex trait mapping using different ethnicities.

Discovery phase in individuals of white European origin. The meta-analysis of sex-combined data from 16 GWAS ($n = 29,347$) of individuals of white European descent identified ten loci associated with adiponectin levels at $p \leq 5.0 \times 10^{-8}$ (Table 1 and Figure 1A and Figure S1, Table S2). These results include the previously described associations with adiponectin at *ADIPOQ* (rs6810075[T]; $\beta = 0.06$, p -value = 3.60×10^{-41}), *KNG1* (rs2062632[T]; $\beta = 0.05$, p -value = 2.52×10^{-19}) on 3q27.3, and *CDH13* (rs12922394[T]; $\beta = -0.1$, $p = 3.16 \times 10^{-18}$) on 16q23.3 (Table 1). Furthermore, we identified variants that showed genome-wide significant association in eight novel independent loci including rs9853056 (within the *STAB1* gene), rs4282054 (within the *NT5DC2* gene), rs13083798 (within the *PBRM1* gene), rs1108842 (within the *GNL3* gene), rs11235 (within the *NEK4* gene), rs2710323 (within the *ITIH1* gene), rs3617 (within the *ITIH3* gene), and rs2535627 (within 200 Kb of *ITIH4* gene) at 3p21.1; rs1597466 (within 1 Mb of *TSC22D2* gene) at 3q25.1; rs2980879 (within 1 Mb of *TRIB1* gene) at 8q24.13; rs7955516 (within 1.3 Mb *PDE3A* gene) at 12p12.2; rs601339 (within the *GPR109A* gene) at 12q24.31; rs6488898 (within the *ATP6V0A2* gene), rs7133378 (within the *DNAH10* gene), rs7305864 (within the *CCDC92* gene), and rs7978610 (within the *ZNRF664* gene at 12q24.31, which is 1.3 Mb away from *GPR109A*); rs2925979 (within the *CMIP* at 16q23.2 gene); and rs731839 (within the *PEPD* gene) at 19q13.11. (Figure 2A–2E, Table 1).

In our analysis a common variant (rs601339, MAF = 0.18, allele G) downstream of the *GPR109A* gene (the putative niacin receptor) was associated with adiponectin ($\beta = 0.04$, $p = 7.94 \times 10^{-10}$) and HDL-C ($\beta = 0.03$, $p = 5.59 \times 10^{-7}$) in the global lipid analysis. In a coincident candidate gene analysis 11 SNPs were typed in *GPR109A/B* in CoLaus and LIPOLIP cohorts, containing individuals of European descent. A single nominally significant coding SNP R311C (rs7314976, MAF = 0.14) within the *GPR109A* gene was taken forward for replication and found to be consistently associated with adiponectin in the three cohorts (CoLaus, Fenland and MRC Ely study, $n = 8285$, $p = 4.6 \times 10^{-8}$) and HDL-cholesterol (HDL-C) in four cohorts (CoLaus, Fenland, Ely study and LIPOLIP, $n = 18425$, $p = 2.9 \times 10^{-8}$) (Figure S2A, S2B). However R311C and rs601339 were not in linkage disequilibrium with each other ($r^2 = 0.04$). Therefore the two variants represent two independent signals from the same locus but with similar effects on HDL-cholesterol and adiponectin.

In silico follow-up phase. In the *in-silico* follow-up phase 468 SNPs demonstrating genome-wide significant ($p < 5 \times 10^{-8}$) or suggestive ($p < 5 \times 10^{-6}$) association with adiponectin in the discovery phase were tested for association in additional European cohorts. (Table S3). These SNPs were tested in seven additional GWAS datasets ($n = 6,623$ from NHS, HPFS, HABC, ERF2, LLS, GARP and ARIC studies) and the combined meta-

Table 1. Lead SNP per Locus for Genome-Wide Significant SNPs Arising from the Sex-Combined Meta-Analysis in European Populations.

Nearest**															
Gene	Lead SNP‡	Region	Chr/position†	EA/NEA¶	EAF¶¶	Beta§	SE	P	I2	n	Beta§	SE	P	I2	n
Discovery Phase Results											Joint Analysis Phase*				
LYPLAL1	rs3001032	1q41	1/217794402	T/C	0.7	−0.02	0.005	1.98E-06	0	29,321	−0.02	0.004	3.60E-08	0	35,930
GNL3	rs1108842	3p21.1	3/52695120	C/A	0.50	0.03	0.004	3.66E-11	0.33	29,338	0.03	0.004	1.39E-13	0.2	35,962
TSC22D2	rs1597466	3q25.1	3/151538251	T/G	0.1	−0.04	0.008	1.88E-08	0	29,319	−0.03	0.007	1.62E-06	0.1	35,794
ADIPOQ	rs6810075	3q27.3	3/188031259	T/C	0.6	0.06	0.005	3.60E-41	0	29,140	0.06	0.004	1.19E-43	0	35,749
VEGFA	rs998584	6q21.1	6/43865874	C/A	0.5	0.03	0.005	5.84E-08	0.3	28,167	0.03	0.005	3.25E-08	0.2	34,108
TRIB1	rs2980879	8q24.13	8/126550657	T/A	0.7	0.03	0.005	1.08E-08	0	24,084	0.03	0.005	7.13E-09	0	30,708
PDE3A	rs7955516	12q12.2	12/20389303	C/A	0.4	0.03	0.005	2.43E-08	0.1	29,178	0.02	0.004	4.45E-08	0	38,276
GPR109A	rs601339	12q24.31	12/121740696	G/A	0.2	0.04	0.006	3.87E-11	0	29,325	0.03	0.005	7.81E-10	0.3	35,947
DNAH10	rs7133378	12q24.31	12/122975455	G/A	0.7	−0.03	0.005	1.29E-09	0	29,223	−0.02	0.004	6.21E-07	0.5	35,697
CMIP	rs2925979	16q23.2	16/80092291	T/C	0.3	−0.04	0.005	1.87E-18	0	29,347	−0.04	0.005	1.21E-20	0	35,970
CDH13	rs12922394	16q23.3	16/81229828	T/C	0.1	−0.10	0.011	3.16E-18	0.3	24,466	−0.08	0.010	1.99E-15	0.4	31,089
PEPD	rs731839	19q13.11	19/38590905	G/A	0.35	−0.04	0.005	2.20E-13	0.03	29,166	−0.03	0.004	7.97E-12	0.4	35,771

All SNPs achieving genome-wide significance in the joint analysis phase are marked in *italics*.

*Joint analysis indicates results from the meta-analysis of discovery and follow-up *in-silico* and *de-novo* phases.

**When possible, plausible biological candidate genes have been listed; otherwise, the closest gene is designated.

‡Lead SNP is the SNP with the lowest *p*-value for each locus.

§Betas are estimated from models using the natural log transformed adiponectin.

¶EA: Effect allele, NEA: Non-effect allele.

¶¶EAF: Effect allele frequency.

doi:10.1371/journal.pgen.1002607.t001

analysis of the discovery and follow-up *in-silico* GWAS datasets detected additional loci on chromosomes 1q41 near the *LYPLAL1* gene (rs3001032, $p = 3.6 \times 10^{-8}$) and chromosome 6p21.1 near the *VEGFA* gene (rs998584, $p = 5.8 \times 10^{-12}$) that reached genome-wide significance. While we confirmed seven loci that had reached genome-wide significance at the discovery stage (Table 1, Figure 2F and 2G, Table S2), two identified loci (3q25.1 and 12q24.31) did not remain genome-wide significant in the joint analysis of discovery and follow-up results.

De novo follow-up phase. Next, in the *de-novo* genotyping follow-up phase, we genotyped 10 SNPs with suggestive evidence of association ($5 \times 10^{-8} < p < 5 \times 10^{-6}$) from the meta-analysis of the discovery and *in-silico* follow-up phases in an additional 3,913 individuals. Meta-analyzing the discovery and 2 follow-up stages identified a SNP in *ARL15* (rs6450176 [G]; $\beta = 0.026$, $p = 5.8 \times 10^{-8}$), which was initially described in a previous GWAS for adiponectin levels (Table S3) [16].

Multi-ethnic meta-analysis. To identify loci influencing adiponectin levels in non-European individuals we performed an additional analysis in 4,232 individuals from an African American population and 1,776 individuals from an East Asian population. In the African American populations, only associations at the *ADIPOQ* locus reached genome-wide significance, while in the East Asian population there was evidence of association at the *ADIPOQ* and *CDH13* loci (Table S4). Subsequently, we performed a meta-analysis that combined all available GWAS including those of white European origin, African American and East Asian ancestry using novel method MANTRA [24]. This analysis identified two additional loci in or near *IRS1* gene on 2q36.3 and at 6q24.1 within a gene desert. (Table 2, Figure 1B).

Secondary GWAS analyses. We next performed meta-analysis of the GWAS data in women ($n = 16,685$) and men

($n = 12,662$) separately (Figure S2A, S2B, Tables S5 and S6). Although no novel loci reached genome-wide significance in women or men separately, three loci (chromosome 3p, 8 and 12) associated with adiponectin levels in the sex-combined analysis showed evidence of association (p value $< 5 \times 10^{-8}$) in women (Figure S3). Since different assays were used to measure adiponectin levels, we next tested whether stratification by assay rendered similar results and found the results were highly concordant with the combined analysis. GWAS for high molecular weight adiponectin in the CHS study ($n = 2,718$) identified 2 SNPs in *ADIPOQ* (rs17300539, $p = 3.0 \times 10^{-16}$) and *CMIP* (rs2927307, $p = 2.7 \times 10^{-8}$). These two genes are located within the loci identified in our discovery meta-analysis of adiponectin levels.

Gene Expression Studies

Through gene expression studies we sought to address two questions: First, are any of the SNPs that were genome-wide significant for adiponectin levels associated with expression of the nearest transcripts (*cis*-eQTLs) and second, whether mRNA levels of loci identified through the GWAS for adiponectin levels are associated with circulating adiponectin levels. To address the first question, we examined whether SNPs within 1 Mb of the SNPs achieving genome-wide significance in the discovery stage were associated with the expression levels of nearby genes in human adipocytes from 776 participants of the MuTHER Consortium [25]. We identified 74 SNPs in three eQTLs to be associated with the expression of five genes in adipocytes, using an array-wide level of statistical significance for eQTLs ($P < 5.1 \times 10^{-5}$. See Materials and Methods for details). These genes included: *NT5DC2* on chromosome 3; *CCDC92*, *GPR109A*, and *ZNRF664* on chromosome 12; and *PEPD* on chromosome 19 (Table 3). The *cis*-eQTL

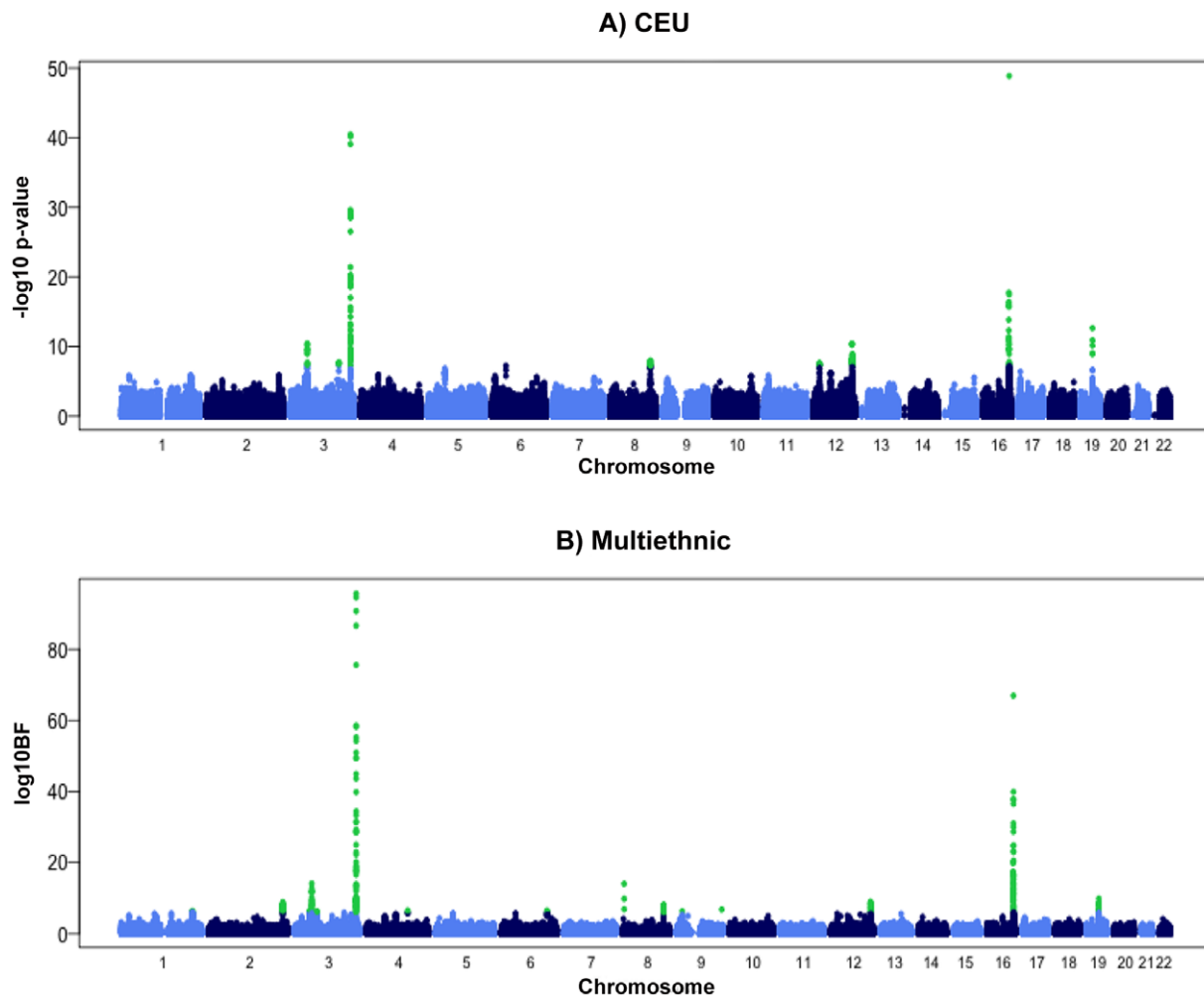


Figure 1. Manhattan plots for meta-analyses in the discovery phase. A) Combined sex analysis in European populations, B) Meta-Analysis of Multiple Ethnicities. The Manhattan plots show $-\log_{10}(p\text{-value})$ measures for association between single nucleotide polymorphisms (SNPs) and chromosomal position. The SNPs that achieved genome-wide significance are highlighted in green.
doi:10.1371/journal.pgen.1002607.g001

SNPs often are proxies for the lead SNPs from the GWAS, however, this relationship may also be influenced through mechanisms that are independent from gene expression, such as gene function.

We next identified that mRNA levels of 18 genes arising from six candidate loci were correlated with circulating adiponectin levels (Table 4). Since circulating adiponectin levels may be associated with a surplus of adipocyte transcripts we next tested for enrichment of signal from the candidate loci. There were 133 transcripts in the identified candidate regions, of which 8.2% (11/133) were associated with adiponectin levels at an array-wide level of significance ($p < 2 \times 10^{-6}$), while 7.5% of the 24k probes on the entire array exceeded the same p-value threshold, indicating there was therefore no additional enrichment of signal at these candidate loci.

T2D and Metabolic Traits

Using data from several large-scale GWAS consortia, some of the significantly associated variants identified here demonstrated associations with T2D and its related traits (Table S7A, S7B, S7C, and S7D). Several individual SNPs showed evidence for association with T2D and various metabolic traits after accounting for the

number of statistically independent SNPs (p-value threshold of 5×10^{-4}) among the SNPs that were genome-wide significant for adiponectin. These include associations with HDL-C ($n = 104$ SNPs), triglycerides (TG) ($n = 65$ SNPs), total cholesterol (TC, $n = 12$ SNPs), LDL-cholesterol (LDL-C, $n = 11$ SNPs), and waist-hip ratio (WHR) ($n = 65$ SNPs) [26]. (However, we note that since sample sizes are different across different consortia power to identify associations is not consistent.) Among these, coding and intronic variants in *STAB1* and *NT5DC2* genes were associated with WHR and HDL-C, while the variants 1 Mb near *TRIB1* were associated with all lipid traits. The coding and intronic variants in the locus on chromosome 12 harboring *ZNF664*, *CCDC92*, and *DNAH10* showed evidence of association with WHR, HDL-C, and TG. Finally, variants in the *PEPD* gene were associated with TG.

We next calculated a multi-SNP genotypic risk score based genome-wide significant SNPs from the discovery phase. This multi-SNP genotypic risk score explained 5% of the variance of natural log-transformed adiponectin levels. We then tested the association of this risk score with risk of T2D and metabolic related traits. The multi-SNP genotypic risk score was associated with increased risk for T2D ($\beta = 0.3$, $p = 4.3 \times 10^{-3}$), where β is the average additive effect of adiponectin-decreasing risk alleles on the

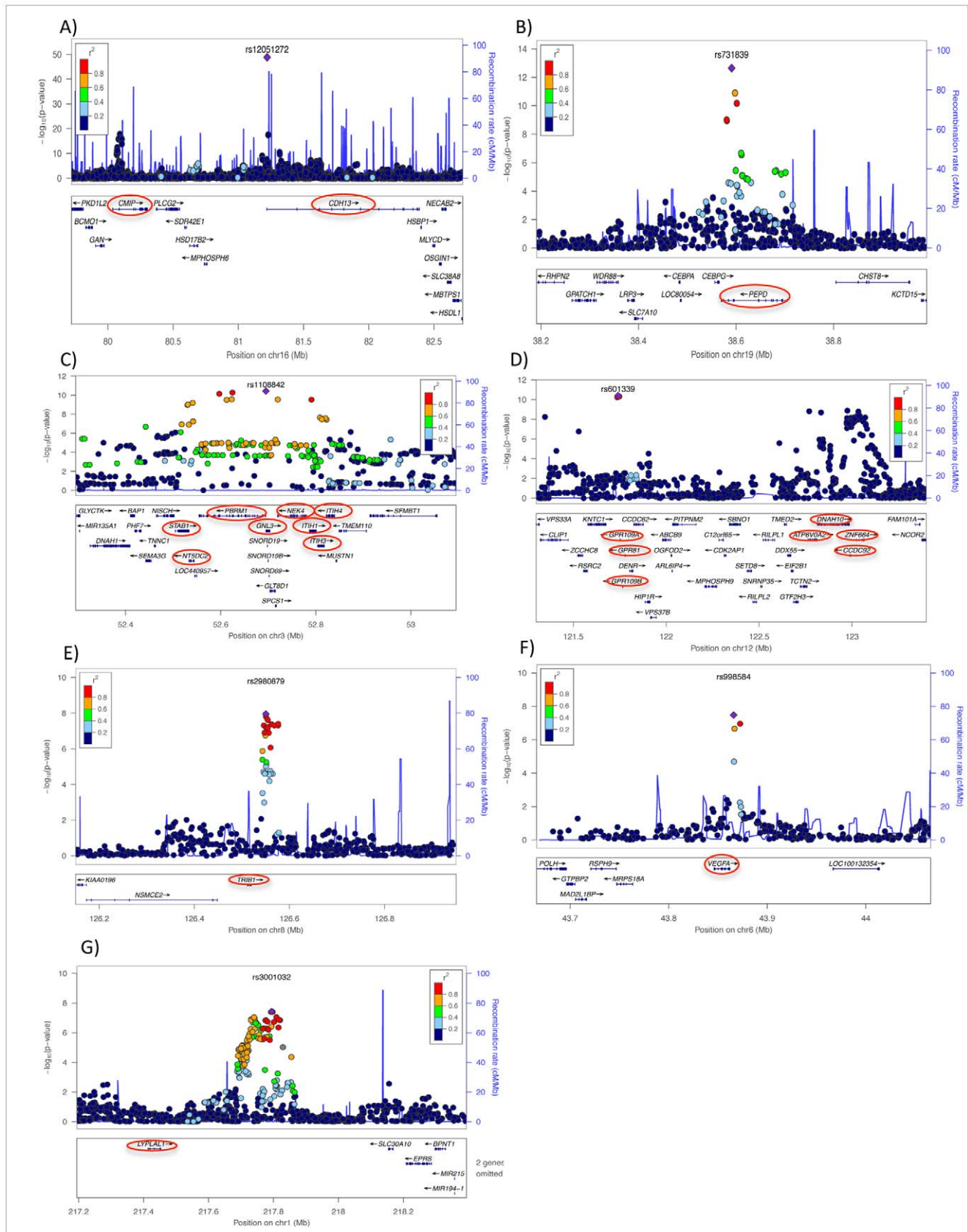


Figure 2. Regional plots of eight newly discovered genome-wide significant chromosomal regions associated with adiponectin concentrations in European populations. A) chromosome 16q23.2, B) chromosome 19 q13.11 C) Chromosome 3p21.1, D) two loci on chromosome 12q24.31, E) chromosome 8q24.13, F) chromosome 6p21.1, and G) chromosome 1q41. In each panel, purple diamonds indicate the top

SNPs, which have the strongest evidence of association. Each circle shows a SNP with a color scale relating the r^2 value for that SNP and the top SNP from HapMap CEU. Blue lines indicate estimated recombination rates from HapMap. The bottom panels illustrate the relative position of genes near each locus. Candidate genes are indicated by red ovals.
doi:10.1371/journal.pgen.1002607.g002

log odds ratio of T2D), increased TG ($\beta = 0.25$, $p = 2.6 \times 10^{-14}$), increased WHR adjusted for BMI ($\beta = 0.18$, $p = 1.8 \times 10^{-5}$), increased post-prandial glucose ($\beta = 0.25$, $p = 0.01$), increased fasting insulin ($\beta = 0.05$, $p = 0.01$), homeostatic model assessment-insulin resistance (HOMA-IR) ($\beta = 0.04$, $p = 0.047$), and with lower HDL-C concentrations ($\beta = -0.24$, $p = 4.5 \times 10^{-13}$) and decreased BMI ($\beta = -0.16$, $p = 1.4 \times 10^{-4}$). (Table 5).

Discussion

In this comprehensive multi-ethnic analysis of the genetic influences on adiponectin levels and their impact on metabolic traits and T2D, we have identified 10 novel loci and confirmed the associations of variants in the *ADIPOQ* and *CDH13* loci with adiponectin levels. The adiponectin risk alleles were associated with T2D and related metabolic traits such as BMI, WHR, TG, HDL-C, 2-hour glucose, HOMA-IR and fasting insulin. These findings demonstrate that adiponectin, T2D and metabolic syndrome have a shared allelic architecture.

Biological Relevance of the GWAS Loci

In the first step toward understanding the biological relevance of the identified regions, we examined the genes harbored by the associated loci using human disease and animal databases. Although some of the genes in these loci do not have a known function, several signify diverse biological functions.

On chromosome 1, the lead SNP was located 300 kb from the *LYPLAL1*, a protein that regulates phospholipids on cellular membranes. Independent efforts have also identified this locus in other metabolic/obesity related traits GWAS: first with WHR (rs2605100; $r^2 = 0.49$ [21] and rs4846567; $r^2 = 0.55$ [27] respectively with the lead adiponectin SNP, rs3001032), and more recently with fasting insulin by a joint meta-analysis including the interaction between SNP and BMI (MF Hivert for the MAGIC investigators, personal communication). In the same report by MAGIC, variants near *IRS1* (insulin receptor substrate 1) and *PEPD* (a protein that hydrolyzes dipeptides and tripeptides) have also been associated with fasting insulin at genome wide significant levels, demonstrating a close link between adiponectin regulation and insulin resistance pathways. Moreover, both *IRS1* and *PEPD* have been associated with T2D (*IRS1* in DIAGRAM [28] and *PEPD* in a Japanese population [29]; $p = 9.3 \times 10^{-12}$ and $p = 1.4 \times 10^{-5}$, respectively).

The lead SNP at 3p21.1 falls within *GML3* that is located in a genomic region containing many genes which could have potential functions in metabolism. Our data provide evidence that adiponectin levels were correlated with human adipocyte mRNA levels of many genes in this region (*GLYCK*, *SEMA3G*, *STAB1*, *PBRM1*, *SFMBT1*; see Table 4). However, this association does not imply a direct influence of these genes on adiponectin level. Among those genes, *STAB1* encodes for stabilin 1, described as an endocytic receptor for advanced glycation end products and may have a function in angiogenesis, lymphocyte homing, cell adhesion, or receptor scavenging for acetylated low-density lipoprotein [30].

Interestingly, several of the genes near lead genome-wide significant SNPs have been implicated in angiogenesis, which might be important for adipose tissue expansion, highlighting the recurring theme of “adipose tissue expandability” in the genetic origins of obesity-related complications [31]. For example, *VEGFA*

is the vascular endothelial growth factor A gene, a known gene in a variety of vascular endothelial cell functions, such as angiogenesis and maintenance of the glomerular endothelium in nephrons [32]. Variants in this gene are also associated with diabetic retinopathy and WHR [27,33]. Moreover, the product of *VEGFA* interacts with resveratrol, which has been shown to have a beneficial influence in some metabolic traits, including diabetes [34]. Rodent studies show that resveratrol decreases blood glucose, blood insulin, and glycated hemoglobin, as well as increases insulin sensitivity in animals with hyperglycemia (reviewed in [35]). Resveratrol also inhibits TNF- α -induced reductions in adiponectin levels in 3T3-L1 adipocytes [36]. Furthermore, it has been shown that resveratrol modulates adiponectin expression and improves insulin sensitivity, likely through the inhibition of inflammatory-like response in adipocytes [37]. At this locus, *VEGFA* mRNA levels in adipocytes were the strongest association with adiponectin levels (Table 4). Also likely involved in vascular biology, *TRIB1* encodes a G protein-coupled receptor-induced protein interacting with MAP kinases that regulates proliferation and chemotaxis of vascular smooth muscle cells [38]. *TRIB1* expression was shown to be elevated in human atherosclerotic arteries [39]. Several variants (rs2954029, rs2954021, rs17321515; all in moderate LD with our lead SNP) in the *TRIB1* gene have been associated with HDL-C, LDL-C and CHD risk in European and Asian populations [22,40,41,42,43]. These two loci (*TRIB1* and *VEGFA*) argue for the importance of vascular biology in adiponectin regulation as underlined previously by findings of adiponectin levels associated with variants near *CDH13* (a receptor for adiponectin expressed by endothelial smooth muscle) [44].

All three homologous genes *GPR109A/B/81* located on chromosome 12 are predominantly expressed in adipocytes and mediate antilipolytic effects [45]. Our eQTL results (Table 3) and the correlation between mRNA and adiponectin levels (Table 4) argue strongly for a role of *GPR109A* at this locus. *GPR109A* (also known as *NIACR1*) is a receptor with a high-affinity, concentration-dependent response to nicotinic acid (niacin) [45]. Treatment by niacin increases serum adiponectin levels by up to 94% in obese men with metabolic syndrome in a time- and dose-dependent manner [46]. Functional studies in *GPR109A* receptor knockout mice demonstrate that niacin increases serum total and HMW adiponectin concentrations and decreases lipolysis following *GPR109A* receptor activation [47]. Moreover, a recent meta-analysis on cohorts containing extremes of HDL-C provided evidence suggestive of association in *GPR109A/B/81* [48].

Finally, variants in *ZNF664* have been associated with CHD, HDL-C and TG levels in a large meta-analysis of over 100,000 individuals of European ancestry [22]. The sex heterogeneity observed in this study is comparable to our finding that the more loci associated with adiponectin at genome wide significance level have been shown in female stratified analysis.

Taken together, the loci identified in this large-scale GWAS for adiponectin levels highlight many genes with demonstrated relationships with metabolic disease.

Shared Allelic Architecture of Adiponectin Levels and Metabolic Traits

Using a multi-SNP genotypic risk score we attempted to understand if the allelic architecture of adiponectin levels was shared with T2D and metabolic traits. This risk score was

Table 2. Genome-Wide Significant SNPs from the Sex-Combined Multi-Ethnic Meta-Analysis.

Nearby* Gene	Lead SNP [‡]	Gene region	chr/position [†]	EA/NEA [¶]	EAF [¶] (CEU/EA/AA)	Multi-Ethnic Fixed Effects Meta-analysis			Multi-Ethnic Random Effects Meta-analysis			MANTRA		N
						Beta (SE)	pvalue	Q-Value	I ²	Beta (SE)	pvalue	BF [§]	phet ^{††}	
LYPLAL1	rs2791553	1q41	1/217742665	G/A	0.6/0.46/0.54	-0.02(0.004)	4.91E-07	25.18	0	-0.02(0.004)	4.91E-07	6.3	0.06	37,665
<i>IRS1</i>	rs925735	2q36.3	2/226887874	G/C	0.64/0.89/0.74	-0.02(0.004)	1.88E-08	22.15	0.01	-0.02(0.004)	2.12E-08	8.1	0.06	37,638
GNL3	rs2590838	3p21.1	3/52597126	G/A	0.5 1/0.34/0.54	-0.03(0.004)	4.08E-15	28.85	0.06	-0.03(0.004)	1.88E-13	14.1	0.05	37,680
ADIPOQ	rs6810075	3q27.3	3/188031259	T/C	0.93/1/0.86	0.06(0.004)	1.10E-43	27.44	0.02	0.06(0.004)	2.41E-42	43.6	0.16	31,533
-	rs592423	6q24.1	6/139882386	C/A	0.54/0.36/0.41	0.02(0.004)	3.59E-07	15.46	0	0.02(0.004)	3.59E-07	6.5	0.03	37,430
TRIB1	rs2980879	8q24.13	8/126550657	T/A	0.69/0.77/0.67	0.03(0.004)	9.91E-10	21.08	0	0.03(0.004)	9.91E-10	8.2	0.04	32,426
GPR109A	rs601339	12q24.31	12/121740696	G/A	0.19/0.39/0.31	0.03(0.005)	3.77E-09	36.11	0.25	0.03(0.006)	4.31E-06	8.3	0.09	37,666
CMIP	rs2925979	16q23.2	16/80092291	T/C	0.3 0/0.43/0.31	-0.04(0.004)	3.12E-21	23.12	0	-0.04(0.004)	3.12E-21	19.8	0.31	37,687
CDH13	rs12051272	16q23.3	16/81220789	T/G	0.03/0.33/0.03	-0.26(0.017)	4.74E-51	39.17	0.62	-0.26(0.032)	1.10E-14	66.0	1.00	24,216
PEPD	rs4805885	19q13.11	19/38597963	T/C	0.39/0.64/0.41	-0.03(0.004)	1.65E-11	34.94	0.23	-0.03(0.005)	2.05E-08	9.9	0.05	37,479

The novel loci identified using Multi-Ethnic Meta-analysis (that were not identified in the European only analysis) are listed in **bold**.

*When possible, plausible biological candidate genes have been listed; otherwise, the closest gene is designated.

†Lead SNP is the SNP with the lowest *p*-value for each locus.

‡Positions are relative to Human Genome NCBI Build 36.

§log₁₀ Bayes factor (BF) from the MANTRA analysis. A log₁₀ BF of 6 and higher was considered as a conservative threshold for genome-wide significance.

††The posterior probability of heterogeneity between studies.

¶EA: effect allele, NEA: non-effect allele.

¶¶EAF: Frequency of effect allele in CEU, East Asian, and AA, populations respectively.

doi:10.1371/journal.pgen.1002607.t002

Table 3. The Association of Lead Genome-Wide Significant SNPs for Adiponectin with mRNA Levels of Their Nearest Gene.

Gene	Lead SNP-Cis-eQTL‡	Chr	Transcript Start Site	Transcript End Site	EA¶	EAF¶¶	Beta (SE)§	P-Exp*	P-GWAS**	lead SNP-GWAS‡‡	r ² §
<i>NT5DC2</i>	rs13081028	3	52533424	52544133	G	0.444	0.14(0.02)	1.32E-19	1.05E-09	rs1108842	0.84
<i>GPR109A</i>	rs2454722*	12	121778105	121781082	G	0.166	-0.15(0.03)	1.71E-09	3.87E-11	rs601339	1
<i>CCDC92</i>	rs10773049	12	122986907	123023116	T	0.611	0.15(0.02)	8.09E-22	2.67E-08	rs7133378	0.02
<i>ZNF664</i>	rs825453	12	123074711	123065922	T	0.615	-0.04(0.01)	4.51E-05	4.03E-08	rs7978610	0.03
<i>PEPD</i>	rs8182584	19	38569694	38704639	T	0.364	-0.13(0.02)	9.96E-10	6.64E-11	rs731839	1

‡Lead SNP is the SNP with the lowest *p*-value for each gene in gene expression data.‡‡Lead SNP is the SNP with the lowest *p*-value for each locus in meta-analysis from discovery phase.

¶EA: Effect allele.

¶¶EAF: Frequency of effect allele.

§Betas are estimated expression levels of the genes.

*P value for lead SNP is the SNP in gene expression data.

**P value for lead SNP in meta-analysis from discovery phase.

§² LD between lead SNP from expression and lead SNP from meta-analysis.

doi:10.1371/journal.pgen.1002607.t003

associated with increased risk of T2D and traits associated with insulin resistance and the metabolic syndrome. However, unexpectedly, adiponectin decreasing alleles were associated with a decrease in BMI. In our adiponectin GWAS, BMI was included as a covariate in order to avoid direct identification of obesity SNPs since BMI is strongly related to adiponectin levels [49,50]. Furthermore, this unexpected direction of effect was entirely explained by SNPs at the *ZNF664* and *PEPD* loci; when these loci were removed from the analysis, the association of the genotypic risk score with BMI disappeared (results not shown). Therefore,

adiponectin risk alleles at *ZNF664* and *PEPD* are of considerable interest since they impart deleterious changes on aspects of the metabolic syndrome (increased TC, TG, LDL-C and WHR and decreased HDL-C), but also act to decrease BMI and percent fat.

Our data do not provide direct evidence as to whether the genetic determinants of adiponectin levels influence these traits through adiponectin itself, or through pleiotropic pathways and therefore do not constitute a Mendelian randomization study. These findings provide a note of caution for Mendelian randomization studies, which may be prone to erroneous conclusions if pleiotropic effects of tested variants are not considered. Nonetheless, in aggregate, these results provide strong evidence that the genetic determinants of adiponectin levels are shared with metabolic disease, and in particular, traits related to insulin resistance.

We note that there are several strengths and limitations of this study. Our main findings, identifying genetic determinants of adiponectin levels, are based on the largest meta-analysis to date and include results from three ethnicities. The availability of expression data from human adipose tissue permitted the association of identified SNPs with mRNA levels at candidate genes and, in turn, correlation of these mRNA levels with circulating adiponectin itself. While access to the data from large consortia permitted assessment of the relevance of the identified SNPs to T2D and components of the metabolic syndrome, we note that a subset of the cohorts included in our GWAS were also included in these external consortia. However, we note that even if we assume that all ADIPOGen study participants were included in the external consortia, for cohorts participating in both studies, that the majority of data in these external consortia still arises from study participants not present in ADIPOGen (minimum percent of non-overlapping subjects: 86.8%, 85.5%, 86.4% and 82.5% for MAGIC, GLGC, GIANT, and DIAGRAM+ consortia, respectively). Therefore, since a substantial majority of participants are independent between ADIPOGen and these consortia, it is unlikely that our findings demonstrating a shared allelic architecture between adiponectin levels and these traits are spurious.

Further, we suggest that locus, 6q24.1, identified only through multi-ethnic meta-analysis using MANTRA and not confirmed through fixed and random effects meta-analysis, be replicated for confirmation of this finding.

In conclusion, the data presented in this study provide strong evidence of association for 10 novel loci for adiponectin levels.

Table 4. The Association of mRNA Levels from Genes in Candidate Loci in Human Adipocytes with Circulating Adiponectin Levels.

Gene	Gene region	GeneStart	GeneEnd	Beta§	Pvalue
<i>GLYCTK</i>	3p21.1	52296875	52304311	0.060	1.77E-20
<i>SEMA3G</i>	3p21.1	52442307	52454083	-0.018	9.28E-06
<i>STAB1</i>	3p21.1	52504395	52533551	-0.039	2.26E-14
<i>PBRM1</i>	3p21.1	52554407	52688779	0.007	2.49E-04
<i>SFMBT1</i>	3p21.1	52913666	53055110	0.010	2.53E-08
<i>DNAJB11</i>	3q27.3	187771160	187786283	-0.014	3.31E-07
<i>EIF4A2</i>	3q27.3	187984054	187990379	0.021	1.53E-08
<i>ADIPOQ</i>	3q27.3	188043156	188058944	0.054	1.03E-13
<i>MAD2L1BP</i>	6q21.1	43711554	43716666	0.009	4.09E-04
<i>VEGFA</i>	6q21.1	43845923	43862199	0.012	2.15E-09
<i>ZCCHC8</i>	12q24.31*	121523387	121551471	0.011	2.60E-04
<i>GPR109B</i>	12q24.31	121765255	121767392	0.010	3.74E-06
<i>GPR109A</i>	12q24.31	121778105	121781082	0.026	1.80E-11
<i>PITPNM2</i>	12q24.31*	122033979	122160928	-0.010	5.09E-06
<i>U1SNRNPBP</i>	12q24.31	122508604	122516894	0.011	1.72E-04
<i>ATP6V0A2</i>	12q24.31	122762817	122812252	-0.008	2.86E-04
<i>ZNF664</i>	12q24.31	123023622	123065922	0.010	8.28E-06
<i>SLC7A10</i>	19q13.11	38391409	38408596	0.072	1.66E-14

§Betas are estimated from log transformed and quantile-quantile normalized values.

*These two loci are independent loci.

doi:10.1371/journal.pgen.1002607.t004

Table 5. Results of Association of Multi-SNP Genotypic Risk Score with Diabetes and Related Traits.

Trait	N	Effect§ (95% CI)	P	Consortium
T2D**	22,044	0.301 (0.09, 0.51)	4.3E-03	DIAGRAM+
BMI (SD units)	121,335	−0.162 (−0.25, −0.08)	1.4E-04	GIANT
WHR*	77,167	0.177 (0.1, 0.26)	1.8E-05	GIANT
Percent Fat	34,853	−0.052 (−0.15, 0.05)	0.31	Body Fat Percent
Fasting Glucose (mmol/L)	46,186	0.011 (−0.03, 0.05)	0.58	MAGIC
Fasting Insulin**(pmol/L)	38,238	0.05 (0.01, 0.09)	1.5E-02	MAGIC
HomaB	36,466	0.033 (0, 0.07)	5.1E-02	MAGIC
Homa IR	37,037	0.042 (0, 0.08)	4.7E-02	MAGIC
2hr Glucose**(mmol/L)	15,234	0.245 (0.06, 0.44)	1.1E-02	MAGIC
HbA1C (%)	35,908	−0.002 (−0.04, 0.03)	0.91	MAGIC
TG**(SD units)	93,440	0.248 (0.18, 0.31)	2.6E-14	GLGC
HDL-C** (SD units)	96,748	−0.243 (−0.31, −0.18)	4.5E-13	GLGC
LDL-C (SD units)	92,348	0.023 (−0.05, 0.09)	0.52	GLGC
TC (SD units)	97,021	0.0003 (−0.07, 0.07)	0.99	GLGC

T2D: Type 2 diabetes, BMI: Body mass Index, WHR: Waist to hip ratio, HbA1C: hemoglobin A1C, TG: Triglyceride, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, TC: Total Cholesterol.

§Effect is mean change in trait or disease per adiponectin-decreasing allele.

*Waist to hip ratio adjusted for BMI.

**Significantly associated trait is coded in bold.

doi:10.1371/journal.pgen.1002607.t005

Further analyses confirmed that the level of expression of some of these candidate genes in human adipocytes correlated directly with adiponectin levels. A multi-SNP genotypic risk score, and several of the identified variants, directly influence parameters of the metabolic syndrome and, in particular, markers of insulin resistance. These findings identify novel genetic determinants of adiponectin levels, which, taken together, influence risk of T2D and markers of insulin resistance.

Materials and Methods

Ethical Consideration

All participants provided informed written consent. The research protocol of all studies were reviewed and approved by institutional ethics review committees at the involved institutions.

Study Design

Our study consisted of three stages. *First*, in the discovery stage we performed a meta-analysis of the GWAS summary statistics of 16 studies involving 29,347 participants of white European origin to detect SNPs that are associated with adiponectin levels. All signals with $p < 5 \times 10^{-6}$ were followed up in seven additional cohorts ($n = 6,623$) with GWAS data (*in-silico* phase) that later joined the consortium and then a subset of SNPs ($n = 10$) by *de-novo* genotyping in 3,913 additional participants from three cohorts ($n = 39,883$ for the combined analysis in Europeans). We also performed a multi-ethnic meta-analysis by combining summary statistics from the 16 studies of individuals of white European discovery cohorts ($n = 29,347$) with those of five cohort studies that included African Americans subjects ($n = 4,232$) and one East Asian cohort ($n = 1,776$) to obtain a total 35,355 individuals for the GWAS meta-analysis involving different ethnicities. After identifying variation near two genes of pharmaceutical importance (*GPR109A* and *GPR109B*), which encode the putative niacin receptors, we typed additional rare coding and tagging variants in a subset of cohorts. *Second*, we examined whether the identified

SNPs of the first stage also associate with mRNA levels of nearest gene(s) expressed using adipose tissue of 776 European women. We also tested for association between adiponectin levels and mRNA levels of the genes in our candidate loci in adipose tissue of a subgroup of 436 individuals [25]. *Third*, we calculated a multi-SNP genotypic risk score using genome-wide significant adiponectin-lowering alleles and tested the association of this risk score with T2D and related metabolic traits. Figure 3 shows a flow chart detailing the study design.

Study Populations

In total, 45,891 individuals from 26 European and 7 non-European cohorts participated in the different phases of this meta-analysis. Participating cohorts were either population-based ($n = 23$), family-based ($n = 4$), or case-control ($n = 4$) studies. The age of participants ranged from 10 to 95 years. Adiponectin levels were measured using ELISA or RIA methods. More details on the study cohorts and adiponectin measurement are presented in the Text S1 and Table S1. In addition, genotyping of four coding and tagging SNPs in the candidate genes, *GRP109A* and *GPR109B*, was undertaken in samples from the Lausanne, Lolipop, MRC Ely, and Fenland cohorts.

Genotyping and Imputation

All cohorts were genotyped using commercially available Affymetrix or Illumina genome-wide genotyping arrays. Quality control was performed for each study independently and genotype imputation was carried out using IMPUTE, MACH, BimBam or Beagle with reference to either the Phase II CEU, CEU+YRI, or CHB+JPT+CEU HapMap according to the origin of population. Imputation of East Asian genotypes was undertaken by first masking genotypes of 200 SNPs and then imputing them based on the CEU+CHB+JPT panel from HapMap. This resulted in an allelic concordance rate of $\sim 96.7\%$. For the African Americans, a combined CEU+YRI reference panel was created. This panel included SNPs segregating in both CEU and YRI, as well as SNPs

segregating in one panel and monomorphic and non-missing in the other (2.74 million SNPs). Due to the overlap of African American individuals on the Affymetrix 6.0 and IBC arrays [51], it was possible to analyze imputation performance at SNPs not genotyped on Affymetrix 6.0. For imputation based on Affymetrix data, the use of the CEU+YRI panel resulted in an allelic concordance rate of $\sim 95.6\%$ (calculated as $1 - 0.5 * [\text{imputed_dosage} - \text{chip_dosage}]$). This rate is comparable to rates calculated for individuals of African descent imputed with the HapMap 2 YRI individuals. Table S1 summarizes the genotyping methods used for each cohort, genotype-calling algorithms, imputation algorithms and exclusion thresholds. SNP-level quality control metrics were applied prior to meta-analysis for each cohort. These were: call rate $\geq 95\%$, minor allele frequency (MAF) $\geq 1\%$, Hardy-Weinberg equilibrium (HWE) $p > 10^{-6}$, and quality measures for imputed SNPs ($r^2 \geq 0.3$, or proper info ≥ 0.4 , for cohorts imputing their data with MACH and IMPUTE, respectively).

Eleven coding and tagging variants in two candidate genes of pharmaceutical importance (*GPR109A* encoding the niacin receptor and *GPR109B*) were genotyped in a parallel study in Lausanne, Lolipop, MRC Ely, and Fenland white subjects. Genotyping was performed using a KASPar-On-Demand SNP Genotyping Assay (KBioscience Ltd., Hoddesdon, UK). In Lausanne and Lolipop samples the genotyping assay was carried out on 3.75 ng of genomic DNA in 1 μ l 1536-well plate reactions, dispensed with a Meridian, microfluidic dispenser (KBioscience Ltd., Hoddesdon, UK), thermocycled using a Hydrocycler (KBioscience Ltd., Hoddesdon, UK). A Pherastar (BMG GmbH, Germany) was used for end-point detection and Kraken-LIMS (KBioscience Ltd., Hoddesdon, UK) was used for automated allele calling. In MRC Ely and Fenland samples, the genotyping assay was carried out on 10 ng of genomic DNA in 5 μ l 384-well plate reactions using a G-Storm GS4 Thermal Cycler (GRI, Rayne, UK). The ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Warrington, UK) was used for end-point detection and allele calling.

Statistical Analysis

Genome-wide association studies. All cohorts independently tested for the additive genetic association of common (MAF $> 1\%$) genotyped and imputed SNPs with natural log transformed adiponectin levels, while adjusting for age, sex, body mass index (BMI), principal components of population stratification and study site (where appropriate), and for family structure in cohorts with family members [49,50,52]. The analyses were performed for men and women combined, as well as for men and women separately. The Cardiovascular Health Study cohort (CHS) also provided GWA results for high molecular weight (HMW) adiponectin using the same methods as described above.

Meta-analysis of GWAS. The meta-analysis was performed by two analysts independently each using different methods; inverse variance-weighted methods using both fixed and random effect models available through either the METAL (<http://www.sph.umich.edu/csg/abecasis/metal/>) or GWAMA version 2.0.5 (<http://www.well.ox.ac.uk/gwama/>) software packages [53]. Summary statistics were crosschecked to ensure consistency of results. Prior to the meta-analysis, study-specific summary statistics were corrected using genomic control (lambda range = 0.99–1.25) and the overall meta-analytic results were additionally corrected for genomic control (lambda = 1.06). To examine whether associations with adiponectin were sex-specific, we performed meta-analyses for men and women separately. A p -value threshold of 5×10^{-8} was considered to be genome-wide significant. Ethnicity-specific meta-analyses were performed for white Euro-

pean and non-European populations separately, using the same methods as described above.

Presence of heterogeneity in the meta-analysis was assessed by the I^2 statistic and Q-test [54]. Since cohorts measured adiponectin concentrations using either RIA or ELISA methods, we also performed a GWA meta-analysis stratified by the method of measurement to test whether this contributed to heterogeneity.

Follow-up phase. The follow-up phase comprised two stages; *in-silico follow-up* and *de-novo follow-up*.

—**In silico follow-up:** 468 SNPs with $p < 5 \times 10^{-6}$ from the discovery phase (which includes both genome-wide significant [$n = 196$, $p < 5 \times 10^{-8}$] and “suggestive” [$n = 272$, $5 \times 10^{-8} < p < 5 \times 10^{-6}$] SNPs Table S3) were tested for their association in 6,623 individuals from seven additional cohorts with GWAS data that joined the consortium after the discovery stage had been finalized.

—**De novo follow-up:** We next selected the lead SNP arising from selected loci from the joint analysis of the discovery and *in-silico* follow-up phase with p -values greater than 5×10^{-8} but less than 5×10^{-6} and genotyped 10 SNPs in 3,164 samples from the SAPHIR cohort and an additional subgroup of the KORA cohort. Finally, these same SNPs, or their proxy SNPs ($n = 2$), were tested for association in the THISEAS cohort ($n = 738$), which had been genotyped using the MetaboChip [55]. Study-level summary statistics from the follow-up phases were meta-analyzed with the data from the discovery phase.

Multi-ethnic meta-analysis. In order to perform a meta-analysis of GWAS data from cohorts of different ethnic backgrounds, we utilized the novel MANTRA (Meta-ANalysis of Trans-ethnic Association studies) software [24]. This method combines GWAS from different ethnic groups by taking advantage of the expected similarity in allelic effects between the most closely related populations. Fixed-effects meta-analysis assumes the allelic effect to be the same in all populations, and cannot account for heterogeneity between ethnic groups. Conversely, random effects meta-analysis assumes that each population has a different underlying allelic effect, however, populations from the same ethnic group would be more homogeneous than those that are more distantly related. To address this challenge we accounted for the expected similarity in allelic effects between the most closely related populations by means of a Bayesian partition model. For each variant, allelic effects and corresponding standard errors are estimated within each population under the assumption of an additive model. Populations are then clustered according to their similarity in terms of relatedness as measured by the mean allele frequency difference at 10,000 independent SNPs, and to their allelic effects at the variant. If all populations are assigned to the same cluster, this is equivalent to a fixed allelic effect across all populations (i.e. no trans-ethnic heterogeneity). The posterior distribution of the allelic effect in each population under the Bayesian partition model is approximated by means of a Monte-Carlo Markov chain algorithm. Evidence in favor of association of the trait with the variant was assessed by means of a Bayes' factor (BF). A log10 BF of 6 or higher is considered a relatively conservative threshold for genome-wide significance. We also performed meta-analysis by using both random and fixed effects models including all ethnicities. Those loci that achieved both a BF > 6 in MANTRA and a P -value less than 5×10^{-7} in multiethnic analysis are presented in Table 2.

Association of Genome-Wide Significant SNPs with Gene Expression (Stage 2)

In order to identify *cis*-expression quantitative trait loci (*cis*-eQTLs) and test whether mRNA levels of candidate genes arising from our GWAS were associated with adiponectin levels, we used

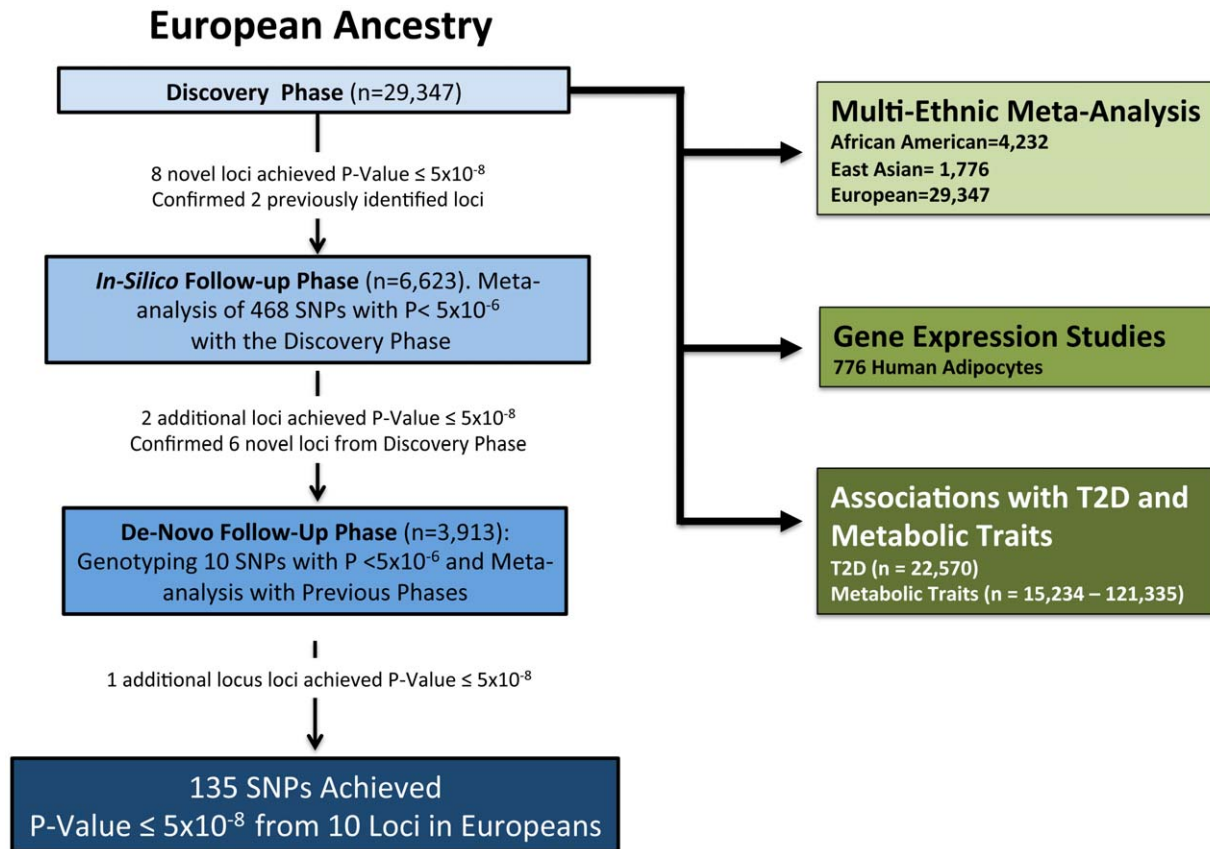


Figure 3. Flow chart of study design.
doi:10.1371/journal.pgen.1002607.g003

expression profiles in human adipocytes from the Multiple Tissue Human Expression Resource (MuTHER) Consortium, (856 female twins from the UK) [25]. mRNA expression profiles from subcutaneous fat and genome-wide genotypes were available for 776 individuals and circulating adiponectin levels for 436 of these women. We note that while adiponectin levels were measured at an earlier time point than the fat biopsies, the BMI at time of adipose expression measurement and time of adiponectin measurement was highly correlated ($r^2 = 0.9$).

cis-eQTLs were defined as associations between SNPs and a transcript within 1 Mb of the identified SNP. To correct for multiple testing, we used QVALUE software [56], and estimated that a genome-wide false discovery rate of 1% corresponds to a p -value threshold of 5.06×10^{-5} (this conservative threshold accounts for all multiple arising from the use of the array, rather than multiple testing arising from assessing only transcripts in the genome-wide significant regions). To test whether mRNA levels of candidate genes identified in the GWAS meta-analysis are associated with circulating adiponectin levels, we applied a Bonferroni corrected threshold of $p < 3 \times 10^{-4}$ (where $3 \times 10^{-4} = 0.05/133$ and 133 was the number of transcripts tested at the candidate loci).

Association of Genome-Wide Significant SNPs with T2D and Metabolic Traits (Stage 3)

The DIAGRAM+ (effective $n = 22,044$) [19], MAGIC ($n =$ up to 46,186) [20], GLGC ($n =$ up to 97,021) [22], GIANT ($n =$ up to 121,335) [21], and Body Fat GWAS ($n =$ up to 36,625) consortia provided summary statistics for the association of each SNP that was genome-wide significant in the discovery phase. Since 196

SNPs (which were estimated to be equivalent to 96 independent statistical tests due to linkage disequilibrium [LD]) [26] were tested for their association, we employed a Bonferroni-corrected threshold of $\alpha = 0.0005$ (where $0.0005 = 0.05/96$) to define the threshold of association for any individual SNP association with T2D and related traits.

While any individual SNP may demonstrate a relationship with T2D or related traits, it can be more informative to test whether a multi-SNP genotypic risk score is associated with the outcome of interest. In the absence of pleiotropic effects arising from loci other than *ADIPOQ*, such a multi-SNP genotypic risk score would enable testing of whether adiponectin levels are causally related to risk of T2D or metabolic traits through a Mendelian randomization framework. Since most of the SNPs that we identified to be genome-wide significant for adiponectin levels were not in the *ADIPOQ* locus, the presence of such pleiotropy precluded a formal Mendelian randomization study. To create a multi-SNP genotypic risk score we implemented a novel method that approximates the average effect of adiponectin decreasing alleles on T2D or related traits. Further, this method allows the use of consortium-level meta-analytic results for a set of SNPs, rather than requiring the re-analysis of individual-level data in each cohort, thereby providing more accurate effects of each allele (due to the larger sample size in the consortium-level meta-analysis). The weighted sum of the individual SNP coefficients leads not only to an estimate of the average combined allelic effect, but also to an approximate estimate of the explained variance (when scaled by the inverse of the total meta-analysis sample size) from a multivariate regression model containing these SNPs.

Specifically, suppose m SNPs have shown association in the discovery phase, and effects are denoted w_i . However, suppose that the goal of interest is to estimate the joint effect of these SNPs on an outcome of interest, y . Let j index the individuals in the outcome of interest dataset and let

$$s_j = \sum_{i=1}^m w_i x_{ij}$$

be a risk score based on the discovery data SNPs, and their associated parameter estimates w_i . Therefore, the desired goal is to estimate the parameter in the following equation: $y_j = y_0 + as_j + e_j$ in the outcome of interest dataset. The proportion of variance in y explained by the previous equation, (i.e. the R^2) attributable to the risk score can be estimated. Standard linear model theory shows that the change in log likelihood is proportional to the R^2 ,

$$2[\ln L(M_1) - \ln L(M_0)] \cong nR^2$$

If the SNPs are uncorrelated, and if the total percentage of variance explained is small, then the change in log likelihood can be approximated by

$$C - \sum_{i=1}^m \frac{(\beta_i - \hat{\beta}_i)^2}{2s_i^2}$$

where β_i now refers to the effect of SNP i in the outcome data, $\hat{\beta}_i$ is the outcome data estimate, and s_i is the associated standard error estimate. Assuming that this log likelihood difference approximation is maximized with an appropriate value of C , then it can be shown that a can be estimated by:

$$\hat{a} \cong \frac{\sum_{i=1}^m w_i \hat{\beta}_i s_i^{-2}}{\sum_{i=1}^m w_i^2 s_i^{-2}}$$

with a standard error estimate of

$$se(\hat{a}) \cong \sqrt{\frac{1}{\sum_{i=1}^m w_i^2 s_i^{-2}}}$$

Therefore, under the assumption of uncorrelated SNPs, their joint effect can be estimated in external data by a weighted mean of the individual SNP effects, weighted by the estimates from the discovery data. All these quantities can be obtained from meta-analysis or summary data, so that individual-level data are not required to obtain these results.

To implement this method, we first selected LD-independent adiponectin associated alleles by LD pruning the set of genome-wide significant adiponectin SNPs from the discovery phase with an LD threshold of $r^2 \leq 0.05$ in the HapMap CEU population, yielding 20 independent LD blocks from the 196 SNPs in Table S2. (We also applied the method using an LD threshold of $r^2 \leq 0.01$ and found no relevant change in results). Since many SNPs from the same independent blocks were associated with adiponectin, we selected the SNP from the LD block that explained the most variance in adiponectin levels. Next, we approximated the effect of the multi-SNP genetic risk score using β and its standard error as derived from the consortium-level meta-analysis in DIAGRAM+, MAGIC, GLGC, GIANT and Body Fat GWAS consortium.

Supporting Information

Figure S1 The comparison between two independent meta-analyses performed in different centers for quality control purposes. The $-\log_{10} p$ -value of all SNPs with $MAF \geq 0.01$ in the first analysis are plotted against the $-\log_{10} p$ -value from the second analysis.

(TIF)

Figure S2 The Manhattan plots of sex-stratified meta-analyses in the discovery phase in the European population. The meta-analysis shown in panel a) is stratified for women and that in panel b) is stratified for men. Manhattan plots demonstrate $-\log_{10}(p\text{-value})$ measures for association between single nucleotide polymorphisms (SNPs) and chromosomal position. The SNPs that achieved genome-wide significance are highlighted in green in the plots. The red ovals identify loci found only in women.

(TIF)

Figure S3 Association Results Near Peaks for Sex-specific Analysis of Adiponectin. SNPs in regions near peak associations are shown for a) chromosome 8 female, b) chromosome 8 males, c) chromosome 12 females and d) chromosome 12 males. Purple diamonds indicate the top SNPs, which have the strongest evidence of association in women. Each circle shows a SNP with a color scale proportional to the r^2 value for that SNP and the top SNP from HapMap CEU. Blue lines show the estimated recombination rates from HapMap. The bottom panels illustrate the relative position of each gene in the locus.

(TIF)

Table S1 Cohort characteristics.

(XLSX)

Table S2 Comparing the Genome-Wide Significant SNPs from fixed effect model with random effect model. *SNP with I^2 less than 0.5 are listed in bold, EA: Effect Allele, NEA: Non-Effect Allele.

(PDF)

Table S3 Association Results of SNPs achieving $p \leq 5 \times 10^{-6}$ in the Discovery phase in European Populations (Sex-Combined Analysis). *Denotes SNPs typed in the *de-novo* follow-up phase.

(PDF)

Table S4 Genome-Wide Significant SNPs ($p < 5 \times 10^{-8}$) Associated with Adiponectin Levels in Non-Europeans Populations. EA: Effect Allele, NEA: Non-Effect Allele, EA-Freq: Frequency of Effect Allele.

(PDF)

Table S5 SNPs associated with adiponectin at genome-wide significant levels ($p < 5 \times 10^{-8}$) using the fixed-effect model in women only in European populations (including Discovery and Follow-Up phases).

(PDF)

Table S6 SNPs associated with adiponectin at genome-wide significant levels ($p < 5 \times 10^{-8}$) using fixed-effect models in men only in European populations.

(PDF)

Table S7 Association results of nominally significant SNPs with Type 2 Diabetes in the DIAGRAM+ Consortium. EA: Effect Allele, NEA: Non-Effect Allele. B) Association results of nominally significant SNPs with diabetes-related traits in the MAGIC Consortium. Fasting glucose and 2 h glucose in mmol/L; Insulin in pmol/L, EA: Effect Allele, NEA: Non-Effect Allele. C) Association results of nominally significant SNPs with diabetes-

related traits in the GIANT and Body fat GWAS consortia. The beta expressed in inverse normally transformed BMI units (i.e. interpretable as SD or Z-score), shows the change in BMI per additional effect allele. *Results that are statistically significant, accounting for the number of independent SNPs, are highlighted in bold., EA: Effect Allele, NEA: Non-Effect Allele, EA-Freq: Frequency of Effect Allele. D) Association results of nominally significant SNPs with lipid traits in the GLGC Consortium. For these traits the effect size is in SD units, based on standard error-weighted meta-analysis. *Results that are statistically significant, accounting for the number of independent SNPs are highlighted in bold., EA: Effect Allele, NEA: Non-Effect Allele, EA-Freq: Frequency of Effect Allele.

(PDF)

Text S1 Supplemental data include description of study cohorts and funding.

(DOCX)

Acknowledgments

We thank all study participants, volunteers, and study personnel that made this consortium possible. We would also like to thank Ms. Renee Atallah for her efforts with the writing and correction of the manuscript.

Consortia Authors' list:

DIAGRAM+:

Benjamin F Voight^{1,2,3}, Laura J Scott⁴, Valgerdur Steinthorsdottir⁵, Andrew P Morris⁶, Christian Dina^{7,8}, Ryan P Welch⁹, Eleftheria Zeggini^{6,10}, Cornelia Huth^{11,12}, Yuri S Aulchenko¹³, Gudmar Thorleifsson⁵, Laura J McCulloch¹⁴, Teresa Ferreira⁶, Harald Grallert^{11,12}, Najaf Amin¹³, Guanming Wu¹⁵, Cristen J Willer⁴, Soumya Raychaudhuri^{1,2,16}, Steve A McCarroll^{1,17}, Claudia Langenberg¹⁸, Oliver M Hofmann¹⁹, Josée Dupuis^{20,21}, Lu Qi²²⁻²⁴, Avellet V Segrè^{1,2,17}, Mandy van Hoek²⁵, Pau Navarro²⁶, Kristin Ardlie⁴, Beverley Balkau^{27,28}, Rafn Benediktsson^{29,30}, Amanda J Bennett¹⁴, Roza Blagieva³¹, Eric Boerwinkle³², Lori L Bonnycastle³³, Kristina Bengtsson Boström³⁴, Bert Bravenboer³⁵, Suzannah Bumpstead¹⁰, Noël P Burt¹, Guillaume Charpentier³⁶, Peter S Chines³³, Marilyn Cornelis²⁴, David J Couper³⁷, Gabe Crawford¹, Alex SF Doney^{38,39}, Katherine S Elliott⁶, Amanda L Elliott^{1,17,40}, Michael R Erdos³³, Caroline S Fox^{21,41}, Christopher S Franklin⁴², Martha Ganser⁴, Christian Gieger¹¹, Niels Grarup⁴³, Todd Green^{1,2}, Simon Griffin¹⁸, Christopher J Groves¹⁴, Candace Guiducci¹, Samy Hadjadj⁴⁴, Neelam Hassanali¹⁴, Christian Herder⁴⁵, Bo Isomaa^{46,47}, Anne U Jackson⁴, Paul RV Johnson⁴⁸, Torben Jorgensen^{49,50}, Wen HL Kao^{51,52}, Norman Klopp¹¹, Augustine Kong⁵, Peter Kraft^{22,23}, Johanna Kuusisto⁵³, Torsten Lauritzen⁵⁴, Man Li⁵¹, Aloysius Lieveise⁵⁵, Cecilia M Lindgren⁶, Valeriya Lyssenko⁵⁶, Michel Marre^{57,58}, Thomas Meitinger^{59,60}, Kristian Midtthjell⁶¹, Mario A Morken³³, Narisu Narisu³³, Peter Nilsson⁵⁶, Katharine R Owen¹⁴, Felicity Payne¹⁰, John RB Perry^{62,63}, Ann-Kristin Petersen¹¹, Carl Platou⁶¹, Christine Proença⁷, Inga Prokopenko^{6,14}, Wolfgang Rathmann⁶⁴, N William Rayner^{6,14}, Neil R Robertson^{6,14}, Ghislain Rocheleau⁶⁵⁻⁶⁷, Michael Roden^{45,68}, Michael J Sampson⁶⁹, Richa Saxena^{1,2,40}, Beverley M Shields^{62,63}, Peter Shrader^{3,70}, Gunnar Sigurdsson^{29,30}, Thomas Sparso⁴³, Klaus Strassburger⁶⁴, Heather M Stringham⁴, Qi Sun^{22,23}, Amy J Swift³³, Barbara Thorand¹¹, Jean Tichet⁷¹, Tiinamaija Tuomi^{46,72}, Rob M van Dam²⁴, Timon W van Haften⁷³, Thijs van Herpt^{25,55}, Jana V van Vliet-Ostapchouk⁷⁴, G Bragi Walters⁵, Michael N Weedon^{62,63}, Cisca Wijmenga⁷⁵, Jacqueline Witteman¹³, Richard N Bergman⁷⁶, Stephane Cauchi⁷, Francis S Collins⁷⁷, Anna L Gloyn¹⁴, Ulf Gyllenstein⁷⁸, Torben Hansen^{43,79}, Winston A Hide¹⁹, Graham A Hitman⁸⁰, Albert Hofman¹³, David J Hunter^{22,23}, Kristian Hveem^{61,81}, Markku Laakso⁵³, Karen L Mohlke⁸², Andrew D Morris^{38,39}, Colin NA Palmer^{38,39}, Peter P Pramstaller⁸³, Igor Rudan^{42,84,85}, Eric Sijbrands²⁵, Lincoln D Stein¹⁵, Jaakko Tuomilehto⁸⁶, Andre Uitterlinden²⁵, Mark Walker⁸⁷, Nicholas J Wareham¹⁸, Richard M Watanabe^{76,88}, Goncalo R Abecasis⁴, Bernhard O Boehm³¹, Harry Campbell⁴², Mark J Daly^{1,2}, Andrew T Hattersley^{62,63}, Frank B Hu²²⁻²⁴, James B Meigs^{3,70}, James S Pankow⁸⁹, Oluf Pedersen^{43,90,91}, H-Erich Wichmann^{11,12,92}, Inês Barroso¹⁰, Jose C Florez^{1,2,3,93}, Timothy M Frayling^{62,63}, Leif Groop^{56,72}, Rob Sladek⁶⁵⁻⁶⁷, Unnur Thorsteinsdottir^{5,94}, James F Wilson⁴², Thomas Illig¹¹,

Philippe Froguel^{7,95}, Cornelia M van Duijn¹³, Kari Stefansson^{5,94}, David Altshuler^{1,2,3,17,40,93}, Michael Boehnke⁴, Mark I McCarthy^{6,14,96}.

1. Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts 02142, USA

2. Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge Street, Boston, Massachusetts 02114, USA

3. Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA

4. Department of Biostatistics, University of Michigan, Ann Arbor, Michigan 48109-2029, USA

5. deCODE Genetics, 101 Reykjavik, Iceland

6. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK

7. CNRS-UMR-8090, Institute of Biology and Lille 2 University, Pasteur Institute, F-59019 Lille, France

8. INSERM UMR915 CNRS ERL3147 F-44007 Nantes, France

9. Bioinformatics Program, University of Michigan, Ann Arbor MI USA 48109

10. Wellcome Trust Sanger Institute, Hinxton, CB10 1HH, UK

11. Institute of Epidemiology, Helmholtz Zentrum Muenchen, 85764 Neuherberg, Germany

12. Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, 81377 Munich, Germany

13. Department of Epidemiology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.

14. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, OX3 7LJ, UK

15. Ontario Institute for Cancer Research, 101 College Street, Suite 800, Toronto, Ontario M5G 0A3, Canada

16. Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA

17. Department of Molecular Biology, Harvard Medical School, Boston, Massachusetts 02115, USA

18. MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK

19. Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts 02115, USA

20. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA

21. National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts 01702, USA

22. Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115, USA

23. Department of Epidemiology, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115, USA

24. Channing Laboratory, Dept. of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Ave, Boston, MA 02115, USA

25. Department of Internal Medicine, Erasmus University Medical Centre, PO-Box 2040, 3000 CA Rotterdam, The Netherlands

26. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU, UK

27. INSERM U780, F-94807 Villejuif, France

28. University Paris-Sud, F-91405 Orsay, France

29. Landspítali University Hospital, 101 Reykjavik, Iceland

30. Icelandic Heart Association, 201 Kopavogur, Iceland

31. Division of Endocrinology, Diabetes and Metabolism, Ulm University, 89081 Ulm, Germany

32. The Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas 77030, USA

33. National Human Genome Research Institute, National Institute of Health, Bethesda, Maryland 20892, USA

34. R&D Centre, Skaraborg Primary Care, 541 30 Skövde, Sweden

35. Department of Internal Medicine, Catharina Hospital, PO-Box 1350, 5602 ZA Eindhoven, The Netherlands

36. Endocrinology-Diabetology Unit, Corbeil-Essonnes Hospital, F-91100 Corbeil-Essonnes, France

37. Department of Biostatistics and Collaborative Studies Coordinating Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, 27599, USA

38. Diabetes Research Centre, Biomedical Research Institute, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, UK

39. Pharmacogenomics Centre, Biomedical Research Institute, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, UK
 40. Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA
 41. Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA
 42. Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, UK
 43. Hagedorn Research Institute, DK-2820 Gentofte, Denmark
 44. Centre Hospitalier Universitaire de Poitiers, Endocrinologie Diabetologie, CIC INSERM 0801, INSERM U927, Université de Poitiers, UFR, Médecine Pharmacie, 86021 Poitiers Cedex, France
 45. Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany
 46. Folkhälsan Research Center, FIN-00014 Helsinki, Finland
 47. Malmka Municipal Health Center and Hospital, 68601 Jakobstad, Finland
 48. Diabetes Research and Wellness Foundation Human Islet Isolation Facility and Oxford Islet Transplant Programme, University of Oxford, Old Road, Headington, Oxford, OX3 7LJ, UK
 49. Research Centre for Prevention and Health, Glostrup University Hospital, DK-2600 Glostrup, Denmark
 50. Faculty of Health Science, University of Copenhagen, 2200 Copenhagen, Denmark
 51. Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland 21287, USA
 52. Department of Medicine, and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland 21287, USA
 53. Department of Medicine, University of Kuopio and Kuopio University Hospital, FIN-70211 Kuopio, Finland
 54. Department of General Medical Practice, University of Aarhus, DK-8000 Aarhus, Denmark
 55. Department of Internal Medicine, Maxima MC, PO-Box 90052, 5600 PD Eindhoven, The Netherlands
 56. Department of Clinical Sciences, Diabetes and Endocrinology Research Unit, University Hospital Malmö, Lund University, 205 02 Malmö, Sweden
 57. Department of Endocrinology, Diabetology and Nutrition, Bichat-Claude Bernard University Hospital, Assistance Publique des Hôpitaux de Paris, 75870 Paris Cedex 18, France
 58. INSERM U695, Université Paris 7, 75018 Paris, France
 59. Institute of Human Genetics, Helmholtz Zentrum Muenchen, 85764 Neuherberg, Germany
 60. Institute of Human Genetics, Klinikum rechts der Isar, Technische Universität München, 81675 Muenchen, Germany
 61. Nord-Trøndelag Health Study (HUNT) Research Center, Department of Community Medicine and General Practice, Norwegian University of Science and Technology, NO-7491 Trondheim, Norway
 62. Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical School, University of Exeter, Magdalen Road, Exeter EX1 2LU, UK
 63. Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, University of Exeter, Barrack Road, Exeter EX2 5DW, UK
 64. Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany
 65. Department of Human Genetics, McGill University, Montreal H3H 1P3, Canada
 66. Department of Medicine, Faculty of Medicine, McGill University, Montreal, H3A 1A4, Canada
 67. McGill University and Genome Quebec Innovation Centre, Montreal, H3A 1A4, Canada
 68. Department of Metabolic Diseases, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany
 69. Department of Endocrinology and Diabetes, Norfolk and Norwich University Hospital NHS Trust, Norwich, NR1 7UY, UK.
 70. General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA
 71. Institut interrégional pour la Santé (IRSA), F-37521 La Riche, France
 72. Department of Medicine, Helsinki University Hospital, University of Helsinki, FIN-00290 Helsinki, Finland
 73. Department of Internal Medicine, University Medical Center Utrecht, 3584 CG Utrecht, The Netherlands
 74. Molecular Genetics, Medical Biology Section, Department of Pathology and Medical Biology, University Medical Center Groningen and University of Groningen, 9700 RB Groningen, The Netherlands
 75. Department of Genetics, University Medical Center Groningen and University of Groningen, 9713 EX Groningen, The Netherlands
 76. Department of Physiology and Biophysics, University of Southern California School of Medicine, Los Angeles, California 90033, USA
 77. National Institute of Health, Bethesda, Maryland 20892, USA
 78. Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, S-751 85 Uppsala, Sweden.
 79. University of Southern Denmark, DK-5230 Odense, Denmark
 80. Centre for Diabetes, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK
 81. Department of Medicine, The Hospital of Levanger, N-7600 Levanger, Norway
 82. Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA
 83. Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso 1, 39100 Bolzano, Italy
 84. Croatian Centre for Global Health, Faculty of Medicine, University of Split, Soltanska 2, 21000 Split, Croatia
 85. Institute for Clinical Medical Research, University Hospital "Sestre Milosrdnice", Vinogradska 29, 10000 Zagreb, Croatia
 86. Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki FIN-00300, Finland,
 87. Diabetes Research Group, Institute of Cellular Medicine, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK
 88. Department of Preventive Medicine, Keck Medical School, University of Southern California, Los Angeles, CA, 90089-9001, USA
 89. Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota 55454, USA
 90. Department of Biomedical Science, Panum, Faculty of Health Science, University of Copenhagen, 2200 Copenhagen, Denmark
 91. Faculty of Health Science, University of Aarhus, DK-8000 Aarhus, Denmark
 92. Klinikum Grosshadern, 81377 Munich, Germany
 93. Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts 02144, USA
 94. Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland
 95. Genomic Medicine, Imperial College London, Hammersmith Hospital, W12 0NN, London, UK
 96. Oxford National Institute for Health Research Biomedical Research Centre, Churchill Hospital, Old Road Headington, Oxford, OX3 7LJ, UK
- MAGIC Consortium:**
- Josée Dupuis^{1,2,178}, Claudia Langenberg^{3,178}, Inga Prokopenko^{4,5,178}, Richa Saxena^{6,7,178}, Nicole Soranzo^{8,9,178}, Anne U Jackson¹⁰, Eleanor Wheeler¹¹, Nicole L Glazer¹², Nabila Bouatia-Naji¹³, Anna L Gloyn⁴, Cecilia M Lindgren^{4,5}, Reedik Mägi^{4,5}, Andrew P Morris⁵, Joshua Randall⁵, Toby Johnson^{14–16}, Paul Elliott^{17,176}, Denis Rybin¹⁸, Gudmar Thorleifsson¹⁹, Valgerdur Steinthorsdottir¹⁹, Peter Henneman²⁰, Harald Grallert²¹, Abbas Dehghan²², Jouke Jan Hottenga²³, Christopher S Franklin²⁴, Pau Navarro²⁵, Kijoung Song²⁶, Anuj Goel^{3,27}, John R B Perry²⁸, Josephine M Egan²⁹, Taina Lajunen³⁰, Niels Grarup³¹, Thomas Sparso³¹, Alex Doney³², Benjamin F Voight^{6,7}, Heather M Stringham¹⁰, Man Li³³, Stavroula Kanoni³⁴, Peter Shrader³⁵, Christine Cavalcanti-Proença¹³, Meena Kumari³⁶, Lu Q³⁷, Nicholas J Timpson³⁸, Christian Gieger²¹, Carina Zaben³⁹, Ghislain Rocheleau^{40,41}, Erik Ingelsson^{42,43}, Ping An⁴⁴, Jeffrey O'Connell⁴⁵, Jian'an Luan³, Amanda Elliott^{6,7}, Steven A McCarroll^{6,7}, Felicity Payne¹¹, Rosa Maria Roccaseca¹¹, François Pattou⁴⁶, Praveen Sethupathy⁴⁷, Kristin Ardlie⁴⁸, Yavuz Ariyurek⁴⁹, Beverley Balkau⁵⁰, Philip Barter⁵¹, John P Beilby^{52,53}, Yoav Ben-Shlomo⁵⁴, Rafn Benediktsson^{55,56}, Amanda J Bennett⁴, Sven Bergmann^{14,16}, Murielle Bochud¹⁵, Eric Boerwinkle⁵⁷, Amélie Bonnefond¹³, Lori L Bonnycastle⁴⁷, Knut Borch-Johnsen^{58,59}, Yvonne Böttcher⁶⁰, Eric Brunner³⁶, Suzannah J Bumpstead⁸, Guillaume Charpentier⁶¹, Yii-Der Ida Chen⁶², Peter Chines⁴⁷, Robert Clarke⁶³, Lachlan J McCoin¹⁷, Matthew N Cooper⁶⁴, Marilyn Cornelis³⁷, Gabe Crawford⁶, Laura Crisponi⁶⁵, Ian NMDay³⁸,

- Eco J Cde Geus²³, Jerome Delplanque¹³, Christian Dina¹³, Michael R Erdos⁴⁷, Annette CFedson^{64,66}, Antje Fischer-Rosinsky^{67,68}, Nita GForouhi³, Caroline SFox^{2,69}, Rune Frants⁷⁰, Maria Grazia Franzosi⁷¹, Pilar Galan⁷², Mark OGoodarzi⁶², Jürgen Graessler⁷³, Christopher J Groves⁴, Scott Grundy⁷⁴, Rhian Gwilliam⁸, Ulf Gyllenstein⁷⁵, Samy Hadjadj⁷⁶, Göran Hallmans⁷⁷, Naomi Hammond⁸, Xijing Han¹⁰, Anna-Liisa Hartikainen⁷⁸, Neelam Hassanali⁴, Caroline Hayward²⁵, Simon CHeath⁷⁹, Serge Herberg⁸⁰, Christian Herder⁸¹, Andrew A Hicks⁸², David R Hillman^{66,83}, Aroon DHingorani³⁶, Albert Hofman²², Jennie Hui^{52,84}, Joe Hung^{85,86}, Bo Isomaa^{87,88}, Paul R V Johnson^{4,89}, Torben Jørgensen^{90,91}, Antti Jula⁹², Marika Kaakinen⁹³, Jaakko Kaprio^{94–96}, Y Antero Kesaniemi⁹⁷, Mika Kivimäki³⁶, Beatrice Knight⁹⁸, Seppo Koskinen⁹⁹, Peter Kovacs¹⁰⁰, Kirsten Ohm Kyvik¹⁰¹, GMark Lathrop⁷⁹, Debbie A Lawlor³⁸, Olivier Le Bacquer¹³, Cécile Lecoeur¹³, Yun Li¹⁰, Valeriya Lyssenko¹⁰², Robert Mahley¹⁰³, Massimo Mangino⁹, Alisa KManning¹, Maria Teresa Martínez-Larrad³⁹, Jarred B McAteer^{6,104,105}, Laura J McCulloch⁴, Ruth McPherson¹⁰⁶, Christa Meisinger²¹, David Melzer²⁸, David Meyre¹³, Braxton DMitchell⁴⁵, Mario A Morken⁴⁷, Sutapa Mukherjee^{66,83}, Silvia Naitza⁶⁵, Narisu Narisu⁴⁷, Matthew J Neville^{4,107}, Ben A Oostra¹⁰⁸, Marco Orru⁶⁵, Ruth Pakyz⁴⁵, Colin NA Palmer¹⁰⁹, Giuseppe Paolisso¹¹⁰, Cristian Pattaro⁸², Daniel Pearson⁴⁷, John F Peden^{5,27}, Nancy LPedersen⁴², Markus Perola^{96,111,112}, Andreas F H Pfeiffer^{67,68}, Irene Pichler⁸², Ozren Polasek¹¹³, Danielle Posthuma^{23,114}, Simon CPotter⁵, Anneli Pouta¹¹⁵, Michael A Province⁴⁴, Bruce MPsaty^{116,117}, Wolfgang Rathmann¹¹⁸, Nigel WRayner^{4,5}, Kenneth Rice¹¹⁹, Samuli Ripatti^{96,111}, Fernando Rivadeneira¹²⁰, Michael Roden^{81,121}, Olov Rolandsson¹²², Anneli Sandbaek¹²³, Manjinder Sandhu^{3,124}, Serena Sanna⁶⁵, Avan Aihie Sayer¹²⁵, Paul Scheet¹²⁶, Laura J Scott¹⁰, Udo Seedorf¹²⁷, Stephen J Sharp³, Beverley Shields⁹⁸, Gunnar Sigurdsson^{55,56}, Eric J GSijbrand^{22,120}, Angela Silveira¹²⁸, Laila Simpson^{64,66}, Andrew Singleton¹²⁹, Nicholas LSmith^{130,131}, Ulla Sovio¹⁷, Amy Swift⁴⁷, Holly Syddall¹²⁵, Ann-Christine Syvänen¹³², Toshiko Tanaka^{133,134}, Barbara Thorand²¹, Jean Tichet¹³⁵, Anke Tönjes^{60,136}, Tiinamaija Tuomi^{87,137}, André Gutterlinden^{22,120}, Ko Willems van Dijk^{70,138}, Mandy van Hoek¹²⁰, Dhiraj Varma⁸, Sophie Visvikis-Siest¹³⁹, Veronique Vitart²⁵, Nicole Vogelzangs¹⁴⁰, Gérard Waeber¹⁴¹, Peter J Wagner^{96,111}, Andrew Walley¹⁴², GBragi Walters¹⁹, Kim L Ward^{64,66}, Hugh Watkins^{5,27}, Michael N Weedon²⁸, Sarah H Wild²⁴, Gonneke Willemssen²³, Jaqueline CMWittman²², John WGYarnell¹⁴³, Eleftheria Zeggini^{5,8}, Diana Zelenika⁷⁹, Björn Zethelius^{43,144}, Guangju Zhai⁹, Jing Hua Zhao³, MCarola Zillikens¹²⁰, DIAGRAM Consortium¹⁴⁵, GIANT Consortium¹⁴⁵, Global BPgen Consortium¹⁴⁵, Ingrid B Borecki⁴⁴, Ruth J F Loos³, Pierre Meneton⁸⁰, Patrik KEMagnusson⁴², David MNathan^{104,105}, Gordon H Williams^{69,105}, Andrew THattersley⁹⁸, Kaisa Silander^{96,111}, Veikko Salomaa¹⁴⁶, George Davey Smith³⁸, Stefan R Bornstein⁷³, Peter Schwarz⁷³, Joachim Spranger^{67,68}, Fredrik Karpe^{4,107}, Alan R Shuldiner⁴⁵, Cyrus Cooper¹²⁵, George V Dedoussis³⁴, Manuel Serrano-Rios³⁹, Andrew DMorris¹⁰⁹, Lars Lind¹³², Lyle J Palmer^{64,66,84}, Frank B Hu^{47,148}, Paul WFranks¹⁴⁹, Shah Ebrahim¹⁵⁰, Michael Marmot³⁶, WH Linda Kao^{33,151,152}, James SPankow¹⁵³, Michael J Sampson¹⁵⁴, Johanna Kuusisto¹⁵⁵, Markku Laakso¹⁵⁵, Torben Hansen^{31,156}, Oluf Pedersen^{31,59,157}, Peter Paul Pramstaller^{82,158,159}, H Erich Wichmann^{21,160,161}, Thomas Illig²¹, Igor Rudan^{24,162,163}, Alan F Wright²⁵, Michael Stummvoll⁶⁰, Harry Campbell²⁴, James F Wilson²⁴, Anders Hamsten on behalf of Procardis Consortium¹²⁸, Richard NBERgman¹⁶⁴, Thomas A Buchanan^{164,165}, Francis SCollins⁴⁷, Karen LMohleke¹⁶⁶, Jaakko Tuomilehto^{94,167, 168}, Timo TValle¹⁶⁷, David Altschuler^{6,7,104,105}, Jerome I Rotter⁶², David SSiscovick¹⁶⁹, Brenda WJ H Penninx¹⁴⁰, Dorret I Boomsma²³, Panos Deloukas⁸, Timothy DSpector^{8,9}, Timothy MFrayingling²⁸, Luigi Ferrucci¹⁷⁰, Augustine Kong¹⁹, Unnur Thorsteinsdottir^{19,171}, Kari Stefansson^{19,171}, Cornelia Myan Duijn²², Yuri SAulchenko²², Antonio Cao⁶⁵, Angelo Scuteri^{172,177}, David Schlessinger⁴⁷, Manuela Uda⁶⁵, Aimo Ruokonen¹⁷³, Marjo-Riitta Jarvelin^{17,93, 174}, Dawn MWaterworth²⁶, Peter Vollenweider¹⁴¹, Leena Peltonen^{8,48,96,111,112}, Vincent Mooser²⁶, Goncalo R Abecasis¹⁰, Nicholas J Wareham³, Robert Sladek^{40,41}, Philippe Froguel^{13,142}, Richard MWatanabe^{164,175}, James B Meigs^{35,105}, Leif Groop¹⁰², Michael Boehnke¹⁰, Mark I McCarthy^{4,5,107}, Jose CFlorez^{6,7,104,105} & Inês Barroso¹¹ for the MAGIC investigators
- 1 Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA.
 - 2 National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA.
 - 3 Medical Research Council (MRC), Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK.
 - 4 Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK.
 - 5 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
 - 6 Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA.
 - 7 Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA.
 - 8 Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK.
 - 9 Twin Research and Genetic Epidemiology Department, King's College London, St Thomas' Hospital Campus, London, UK.
 - 10 Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA.
 - 11 Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK.
 - 12 Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington, USA.
 - 13 Centre National de la Recherche Scientifique–Unité Mixte de Recherche 8090, Pasteur Institute, Lille 2–Droit et Santé University, Lille, France.
 - 14 Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland.
 - 15 University Institute of Social and Preventative Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland.
 - 16 Swiss Institute of Bioinformatics, Lausanne, Switzerland.
 - 17 Department of Epidemiology and Public Health, Imperial College London, Faculty of Medicine, Norfolk Place, London, UK.
 - 18 Boston University Data Coordinating Center, Boston, Massachusetts, USA.
 - 19 deCODE Genetics, Reykjavik, Iceland.
 - 20 Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands.
 - 21 Institute of Epidemiology, Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Neuherberg, Germany.
 - 22 Department of Epidemiology, Erasmus Medical College, Rotterdam, The Netherlands.
 - 23 Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands.
 - 24 Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK.
 - 25 MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, UK.
 - 26 Division of Genetics, Research and Development, GlaxoSmithKline, King of Prussia, Pennsylvania, USA.
 - 27 Department of Cardiovascular Medicine, University of Oxford, Oxford, UK.
 - 28 Genetics of Complex Traits, Institute of Biomedical and Clinical Sciences, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK.
 - 29 National Institute of Aging, Baltimore, Maryland, USA.
 - 30 Unit for Child and Adolescent Health and Welfare, National Institute for Health and Welfare, Biocenter Oulu, University of Oulu, Oulu, Finland.
 - 31 Hagedorn Research Institute, Gentofte, Denmark.
 - 32 Department of Medicine and Therapeutics, Level 7, Ninewells Hospital and Medical School, Dundee, UK.
 - 33 Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA.
 - 34 Department of Nutrition–Dietetics, Harokopio University, Athens, Greece.
 - 35 General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA.
 - 36 Department of Epidemiology and Public Health, University College London, London, UK.
 - 37 Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
 - 38 MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol, Bristol, UK.
 - 39 Fundación para la Investigación Biomédica del Hospital Clínico San Carlos, Madrid, Spain.
 - 40 Departments of Medicine and Human Genetics, McGill University, Montreal, Canada.



- 41 Genome Quebec Innovation Centre, Montreal, Canada.
- 42 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.
- 43 Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden.
- 44 Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, Missouri, USA.
- 45 Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland, USA.
- 46 INSERM U 859 , Université de Lille-Nord de France, Lille, France.
- 47 Genome Technology Branch, National Human Genome Research Institute, Bethesda, Maryland, USA.
- 48 The Broad Institute, Cambridge, Massachusetts, USA.
- 49 Leiden Genome Technology Center, Leiden University Medical Center, Leiden, The Netherlands.
- 50 INSERM U 780 , Paris Sud University, Villejuif, France.
- 51 The Heart Research Institute, Sydney, New South Wales, Australia.
- 52 PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands West Australia, Australia.
- 53 School of Surgery and Pathology, University of Western Australia, Nedlands West Australia, Australia.
- 54 Department of Social Medicine, University of Bristol, Bristol, UK.
- 55 Landspítali University Hospital, Reykjavik, Iceland.
- 56 Icelandic Heart Association, Kopavogur, Iceland.
- 57 The Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas, USA.
- 58 Steno Diabetes Center, Gentofte, Denmark.
- 59 Faculty of Health Science, University of Aarhus, Aarhus, Denmark.
- 60 Department of Medicine, University of Leipzig, Leipzig, Germany.
- 61 Endocrinology–Diabetology Unit, Corbeil-Essonnes Hospital, Essonnes, France.
- 62 Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA.
- 63 Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK.
- 64 Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Perth, Australia.
- 65 Istituto di Neurogenetica e Neurofarmacologia (INN), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari, Italy.
- 66 Western Australian Sleep Disorders Research Institute, Queen Elizabeth Medical Centre II, Perth, Australia.
- 67 Department of Endocrinology, Diabetes and Nutrition, Charité-Universitätsmedizin Berlin, Berlin, Germany.
- 68 Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany.
- 69 Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
- 70 Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands.
- 71 Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy.
- 72 Institut National de la Santé et de la Recherche Médicale, Institut National de la Recherche Agronomique, Université Paris 13 , Bobigny Cedex, France.
- 73 Department of Medicine III, Division Prevention and Care of Diabetes, University of Dresden, Dresden, Germany.
- 74 Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas, USA.
- 75 Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden.
- 76 Centre Hospitalier Universitaire, de Poitiers, Endocrinologie Diabétologie, CIC INSERM 0802, INSERM U927, Université de Poitiers, Unité de Formation et de Recherche, Médecine Pharmacie, Poitiers, France.
- 77 Department of Public Health and Clinical Medicine, Section for Nutritional Research, Umeå University, Umeå, Sweden.
- 78 Department of Clinical Sciences, Obstetrics and Gynecology, University of Oulu, University of Oulu, Finland.
- 79 Centre National de Génotypage/Institut de génomique/Commissariat à l'énergie atomique, Evry Cedex, France.
- 80 INSERM U872, Faculté de Médecine Paris Descartes, Paris Cedex, France.
- 81 Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
- 82 Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso, Bolzano, Italy, Affiliated Institute of the University Lübeck, Lübeck, Germany.
- 83 Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Perth, Australia.
- 84 Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Perth, Australia.
- 85 Heart Institute of Western Australia, Sir Charles Gairdner Hospital, Nedlands West Australia, Australia.
- 86 School of Medicine and Pharmacology, University of Western Australia, Nedlands West Australia, Australia.
- 87 Folkhalsan Research Centre, Helsinki, Finland.
- 88 Malmiska Municipal Health Care Center and Hospital, Jakobstad, Finland.
- 89 Nuffield Department of Surgery, University of Oxford, Oxford, UK.
- 90 Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark.
- 91 Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark.
- 92 National Institute for Health and Welfare, Unit of Population Studies, Turku, Finland.
- 93 Institute of Health Sciences and Biocenter Oulu, University of Oulu, Oulu, Finland.
- 94 Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland.
- 95 National Institute for Health and Welfare, Unit for Child and Adolescent Mental Health, Helsinki, Finland.
- 96 Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland.
- 97 Department of Internal Medicine and Biocenter Oulu, Oulu, Finland.
- 98 Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK.
- 99 National Institute for Health and Welfare, Unit of Living Conditions, Health and Wellbeing, Helsinki, Finland.
- 100 Interdisciplinary Centre for Clinical Research, University of Leipzig, Leipzig, Germany.
- 101 The Danish Twin Registry, Epidemiology, Institute of Public Health, University of Southern Denmark, Odense, Denmark.
- 102 Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, University Hospital Malmö, Malmö, Sweden.
- 103 Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, California, USA.
- 104 Diabetes Research Center, Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
- 105 Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
- 106 Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.
- 107 Oxford National Institute for Health Research, Biomedical Research Centre, Churchill Hospital, Oxford, UK.
- 108 Department of Clinical Genetics, Erasmus Medical College, Rotterdam, The Netherlands.
- 109 Biomedical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK.
- 110 Department of Geriatric Medicine and Metabolic Disease, Second University of Naples, Naples, Italy.
- 111 National Institute for Health and Welfare, Unit of Public Health Genomics, Helsinki, Finland.
- 112 Department of Medical Genetics, University of Helsinki, Helsinki, Finland.
- 113 Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Stampar School of Public Health, Medical School, University of Zagreb, Rockefellerova, Zagreb, Croatia.
- 114 Department of Clinical Genetics, VU University and Medical Center, Amsterdam, The Netherlands.

- 115 Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu, Finland.
- 116 Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, Washington, USA.
- 117 Group Health Research Institute, Group Health Cooperative, Seattle, Washington, USA.
- 118 Institute of Biometrics and Epidemiology, German Diabetes Centre, Leibniz Centre at Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
- 119 Department of Biostatistics, University of Washington, Seattle, Washington, USA.
- 120 Department of Internal Medicine, Erasmus Medical College, Rotterdam, The Netherlands.
- 121 Department of Metabolic Diseases, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
- 122 Department of Public Health and Clinical Medicine, Section for Family Medicine, Umeå University, Umeå, Sweden.
- 123 School of Public Health, Department of General Practice, University of Aarhus, Aarhus, Denmark.
- 124 Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK.
- 125 MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, UK.
- 126 Department of Epidemiology, University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA.
- 127 Leibniz-Institut für Arterioskleroseforschung an der Universität Münster, Münster, Germany.
- 128 Atherosclerosis Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.
- 129 Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland, USA.
- 130 Department of Epidemiology, University of Washington, Seattle, Washington, USA.
- 131 Seattle Epidemiologic Research and Information Center, Department of Veterans Affairs Office of Research and Development, Seattle, Washington, USA.
- 132 Department of Medical Sciences, Uppsala University, Uppsala, Sweden.
- 133 Medstar Research Institute, Baltimore, Maryland, USA.
- 134 Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, USA.
- 135 Institut interrégional pour la santé (IRSA), La Riche, France.
- 136 Coordination Centre for Clinical Trials, University of Leipzig, Leipzig, Germany.
- 137 Department of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland.
- 138 Department of Internal Medicine, Leiden University Medical Centre, Leiden, The Netherlands.
- 139 Research Unit, Cardiovascular Genetics, Nancy University Henri Poincaré, Nancy, France.
- 140 EMGO Institute for Health and Care Research, Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands.
- 141 Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.
- 142 Genomic Medicine, Imperial College London, Hammersmith Hospital, London, UK.
- 143 Epidemiology and Public Health, Queen's University Belfast, Belfast, UK.
- 144 Medical Products Agency, Uppsala, Sweden.
- 145 See Supplementary Note for a full list of authors.
- 146 National Institute for Health and Welfare, Unit of Chronic Disease Epidemiology and Prevention, Helsinki, Finland.
- 147 Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
- 148 Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.
- 149 Genetic Epidemiology and Clinical Research Group, Department of Public Health and Clinical Medicine, Section for Medicine, Umeå University Hospital, Umeå, Sweden.
- 150 London School of Hygiene and Tropical Medicine, London, UK.
- 151 Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA.
- 152 The Welch Center for Prevention, Epidemiology, and Clinical Research, School of Medicine and Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA.
- 153 Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA.
- 154 Department of Endocrinology and Diabetes, Norfolk and Norwich University Hospital National Health Service Trust, Norwich, UK.
- 155 Department of Medicine, University of Kuopio and Kuopio University Hospital, Kuopio, Finland.
- 156 Faculty of Health Science, University of Southern Denmark, Odense, Denmark.
- 157 Institute of Biomedical Science, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark.
- 158 Department of Neurology, General Central Hospital, Bolzano, Italy.
- 159 Department of Neurology, University of Lübeck, Lübeck, Germany.
- 160 Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany.
- 161 Klinikum Grosshadern, Munich, Germany.
- 162 School of Medicine, University of Split, Split, Croatia.
- 163 Gen-Info Ltd., Zagreb, Croatia.
- 164 Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
- 165 Department of Medicine, Division of Endocrinology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
- 166 Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA.
- 167 National Institute for Health and Welfare, Unit of Diabetes Prevention, Helsinki, Finland.
- 168 South Ostrobothnia Central Hospital, Seinäjoki, Finland.
- 169 Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington, USA.
- 170 Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, NIH, Baltimore, Maryland, USA.
- 171 Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
- 172 Lab of Cardiovascular Sciences, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, USA.
- 173 Department of Clinical Sciences/Clinical Chemistry, University of Oulu, University of Oulu, Oulu, Finland.
- 174 National Institute of Health and Welfare, Oulu, Finland.
- 175 Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
- 176 MRC-Health Protection Agency Centre for Environment and Health, Imperial College London, London, UK.
- 177 UOC Geriatria, Istituto Nazionale Ricovero e cura per Anziani (INRCA) IRCCS, Rome, Italy.
- 178 These authors contributed equally to this work. Correspondence should be addressed to M.B. (boehnke@umich.edu), M.I.M. (mark.mccarthy@drf.ox.ac.uk), J.C.F. (jcflorez@partners.org) or I.B. (ib1@sanger.ac.uk).

GLGC Consortium:

Tanya M. Teslovich,^{1, 118}, Kiran Musunuru,^{2, 3, 4, 5, 6, 118}, Albert V. Smith,^{7, 8}, Andrew C. Edmondson,^{9, 10}, Ioannis M. Stylianou,¹⁰, Masahiro Koseki,¹¹, James P. Pirruccello,^{2, 5, 6}, Samuli Ripatti,^{12, 13}, Daniel I. Chasman,^{4, 14}, Cristen J. Willer,¹, Christopher T. Johansen,¹⁵, Sigrid W. Fouchier,¹⁶, Aaron Isaacs,¹⁷, Gina M. Peloso,^{18, 19}, Maja Barbalić,²⁰, Sally L. Ricketts,²¹, Joshua C. Bis,²², Yuri S. Aulchenko,¹⁷, Gudmar Thorleifsson,²³, Mary F. Feitosa,²⁴, John Chambers,²⁵, Marju Orho-Melander,²⁶, Olle Melander,²⁶, Toby Johnson,²⁷, Xiaohui Li,²⁸, Xiuqing Guo,²⁸, Mingyao Li,^{9, 10}, Yoon Shin Cho,²⁹, Min Jin Go,²⁹, Young Jin Kim,²⁹, Jong-Young Lee,²⁹, Taesung Park,^{30, 31}, Kyunga Kim,³², Xueling Sim,³³, Rick Twee-Hee Ong,³⁴, Damien C. Croteau-Chonka,³⁵, Leslie A. Lange,³⁵, Joshua D. Smith,³⁶, Kijoung Song,³⁷, Jing Hua Zhao,³⁸, Xin Yuan,³⁷, Jian'an Luan,³⁸, Claudia Lamina,³⁹, Andreas Ziegler,⁴⁰, Weihua Zhang,²⁵, Robert Y. L. Zee,^{4, 14}, Alan F. Wright,⁴¹, Jacqueline C. M. Witteman,^{17, 42}, James F. Wilson,⁴³, Gonneke Willemsen,⁴⁴, H.-Erich Wichmann,⁴⁵, John B. Whitfield,⁴⁶, Dawn M. Waterworth,³⁷, Nicholas J. Wareham,³⁸, Gérard Waeber,⁴⁷, Peter Vollenweider,⁴⁷, Benjamin F. Voight,^{2, 5}, Veronique Vitart,⁴¹, Andre G. Uitterlinden,^{17, 42, 48}, Manuela Uda,⁴⁹, Jaakko Tuomilehto,⁵⁰, John R. Thompson,⁵¹, Toshiko Tanaka,^{52, 53}, Ida Surakka,^{12, 13}, Heather

- M. Stringham,¹ Tim D. Spector,⁵⁴ Nicole Soranzo,^{54, 55} Johannes H. Smit,⁵⁶ Juha Sinisalo,⁵⁷ Kaisa Silander,^{12, 13} Eric J. G. Sijbrands,^{17, 48} Angelo Scuteri,⁵⁸ James Scott,⁵⁹ David Schlessinger,⁶⁰ Serena Sanna,⁴⁹ Veikko Salomaa,⁵⁰ Juha Saharinen,¹² Chiara Sabatti,⁶¹ Aimo Ruukonen,⁶² Igor Rudan,⁴³ Lynda M. Rose,¹⁴ Robert Roberts,⁶³ Mark Rieder,³⁶ Bruce M. Psaty,⁶⁴ Peter P. Pramstaller,⁶⁵ Irene Pichler,⁶⁵ Markus Perola,^{12, 13} Brenda W. J. H. Penninx,⁵⁶ Nancy L. Pedersen,⁶⁶ Cristian Pattaro,⁶⁵ Alex N. Parker,⁶⁷ Guillaume Pare,⁶⁸ Ben A. Oostra,⁶⁹ Christopher J. O'Donnell,^{4, 19} Markku S. Nieminen,⁵⁷ Deborah A. Nickerson,³⁶ Grant W. Montgomery,⁴⁶ Thomas Meitinger,^{70, 71} Ruth McPherson,⁶³ Mark I. McCarthy,^{72, 73, 74} Wendy McArdle,⁷⁵ David Masson,¹¹ Nicholas G. Martin,⁴⁶ Fabio Marroni,⁷⁶ Massimo Mangino,⁵⁴ Patrik K. E. Magnusson,⁶⁶ Gavin Lucas,⁷⁷ Robert Luben,²¹ Ruth J. F. Loos,³⁸ Marja-Liisa Lokki,⁷⁸ Guillaume Lettre,⁷⁹ Claudia Langenberg,³⁸ Lenore J. Launer,⁸⁰ Edward G. Lakatta,⁶⁰ Reijo Laaksonen,⁸¹ Kirsten O. Kyvik,⁸² Florian Kronenberg,³⁹ Inke R. König,⁴⁰ Kay-Tee Khaw,²¹ Jaakko Kaprio,^{12, 13, 83} Lee M. Kaplan,⁸⁴ Åsa Johansson,⁸⁵ Marjo-Riitta Jarvelin,^{86, 87} A. Cecile J. W. Janssens,¹⁷ Erik Ingelsson,⁶⁶ Wilmar Igl,⁸⁵ G. Kees Hovingh,¹⁶ Jouke-Jan Hottenga,⁴⁴ Albert Hofman,^{17, 42} Andrew A. Hicks,⁸⁵ Christian Hengstenberg,⁸⁸ Iris M. Heid,^{45, 89} Caroline Hayward,⁴¹ Aki S. Havulinna,^{50, 90} Nicholas D. Hastie,⁴¹ Tamara B. Harris,⁸⁰ Talin Haritunians,²⁸ Alistair S. Hall,⁹¹ Ulf Gyllenstein,⁸⁵ Candace Guiducci,⁵ Leif C. Groop,^{26, 92} Elena Gonzalez,⁵ Christian Gieger,⁴⁵ Nelson B. Freimer,⁹³ Luigi Ferrucci,⁹⁴ Jeanette Erdmann,⁹⁵ Paul Elliott,^{86, 96} Kenechi G. Ejebe,⁵ Angela Döring,⁴⁵ Anna F. Dominiczak,⁹⁷ Serkalem Demissie,^{18, 19} Panagiotis Deloukas,⁵⁵ Eco J. C. de Geus,⁴⁴ Ulf de Faire,⁹⁸ Gabriel Crawford,⁵ Francis S. Collins,⁹⁹ Yii-der I. Chen,²⁸ Mark J. Caulfield,²⁷ Harry Campbell,⁴³ Noel P. Burt,⁵ Lori L. Bonnycastle,⁹⁹ Dorret I. Boomsma,⁴⁴ S. Matthijs Boekholdt,¹⁰⁰ Richard N. Bergman,¹⁰¹ Inês Barroso,⁵⁵ Stefania Bandinelli,¹⁰² Christie M. Ballantyne,¹⁰³ Themistocles L. Assimes,¹⁰⁴ Thomas Quertermous,¹⁰⁴ David Altshuler,^{2, 4, 5} Mark Seielstad,³⁴ Tien Y. Wong,¹⁰⁵ E-Shyong Tai,¹⁰⁶ Alan B. Feranil,¹⁰⁷ Christopher W. Kuzawa,¹⁰⁸ Linda S. Adair,¹⁰⁹ Herman A. Taylor Jr,¹¹⁰ Ingrid B. Borecki,²⁴ Stacey B. Gabriel,⁵ James G. Wilson,¹¹⁰ Hilma Holm,²³ Unnur Thorsteinsdottir,^{8, 23} Vilundur Gudnason,^{7, 8} Ronald M. Krauss,¹¹¹ Karen L. Mohlke,³⁵ Jose M. Ordovas,^{112, 113} Patricia B. Munroe,¹¹⁴ Jaspal S. Kooner,⁵⁹ Alan R. Tall,¹¹ Robert A. Hegele,¹⁵ John J.P. Kastelein,¹⁶ Eric E. Schadt,¹¹⁵ Jerome I. Rotter,²⁸ Eric Boerwinkle,²⁰ David P. Strachan,¹¹⁶ Vincent Mosser,³⁷ Kari Stefansson,^{8, 23} Muredach P. Reilly,^{9, 10} Nilesh J. Samani,¹¹⁷ Heribert Schunkert,⁹⁵ L. Adrienne Cupples,^{18, 19, 118} Manjinder S. Sandhu,^{21, 38, 55, 118} Paul M. Ridker,^{4, 14, 118} Daniel J. Rader,^{9, 10, 118} Cornelia M. van Duijn,^{17, 42, 118} Leena Peltonen,¹¹⁹ Gonçalo R. Abecasis,^{1, 118} Michael Boehnke,^{1, 118} & Sekar Kathiresan,
- 1 Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan 48109, USA.
 - 2 Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
 - 3 Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
 - 4 Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA.
 - 5 Broad Institute, Cambridge, Massachusetts 02142, USA.
 - 6 Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA.
 - 7 Icelandic Heart Association, Heart Preventive Clinic and Research Institute, 201 Kopavogur, Iceland.
 - 8 University of Iceland, 101 Reykjavik, Iceland.
 - 9 Cardiovascular Institute, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
 - 10 Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, 19104, USA.
 - 11 Division of Molecular Medicine, Department of Medicine, Columbia University, New York, New York 10032, USA.
 - 12 Institute for Molecular Medicine Finland FIMM, University of Helsinki, FI-00014 Helsinki, Finland.
 - 13 National Institute for Health and Welfare, P.O. Box 104, FI-00251 Helsinki, Finland.
 - 14 Division of Preventive Medicine, Brigham and Women's Hospital, Boston Massachusetts 02215, USA.
 - 15 Robarts Research Institute, University of Western Ontario, London, Ontario N6A 5K8, Canada.
 - 16 Department of Vascular Medicine, Academic Medical Centre at the University of Amsterdam, 1105 AZ Amsterdam, The Netherlands.
 - 17 Department of Epidemiology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
 - 18 Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA.
 - 19 National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, Massachusetts 01702, USA.
 - 20 Human Genetics Center, University of Texas Health Science Center at Houston, Houston, Texas 77030, USA.
 - 21 Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge CB1 8RN, UK.
 - 22 Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington 98101, USA.
 - 23 deCODE Genetics, 101 Reykjavik, Iceland.
 - 24 Division of Statistical Genomics in the Center for Genome Sciences, Washington University School of Medicine, St Louis, Missouri 63108, USA.
 - 25 Department of Epidemiology and Public Health, Imperial College London, London W2 1PG, UK.
 - 26 Department of Clinical Sciences, Lund University, SE-20502, Malmö, Sweden.
 - 27 Clinical Pharmacology and Barts and the London Genome Centre, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London EC1M 6BQ, UK.
 - 28 Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA.
 - 29 Center for Genome Science, National Institute of Health, Seoul 122-701, Republic of Korea.
 - 30 Interdisciplinary Program in Bioinformatics, College of Natural Sciences, Seoul National University, Seoul 151-742, Republic of Korea.
 - 31 Department of Statistics, College of Natural Sciences, Seoul National University, Seoul 151-742, Republic of Korea.
 - 32 Department of Statistics, Sookmyung Women's University, Seoul 140-742, Republic of Korea.
 - 33 Centre for Molecular Epidemiology, National University of Singapore, Singapore, 117597, Republic of Singapore.
 - 34 Genome Institute of Singapore, Singapore 138672, Republic of Singapore.
 - 35 Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA.
 - 36 Department of Genome Sciences, University of Washington, Seattle, Washington 98195, USA.
 - 37 Genetics Division, GlaxoSmithKline R&D, King of Prussia, Pennsylvania 19406, USA.
 - 38 MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.
 - 39 Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Schoepfstrasse 41, A-6020 Innsbruck, Austria.
 - 40 Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, 23562 Lübeck, Germany.
 - 41 MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh EH4 2XU, UK.
 - 42 Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA) and Center of Medical Systems Biology (CMSB), 2300 RC Leiden, The Netherlands.
 - 43 Centre for Population Health Sciences, University of Edinburgh, Edinburgh EH8 9AG, UK.
 - 44 Department of Biological Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands.
 - 45 Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health, 85764 Neuherberg, Germany.
 - 46 Genetic Epidemiology Unit, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia.
 - 47 Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.
 - 48 Department of Internal Medicine, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands.

- 49 Istituto di Neurogenetica e Neurofarmacologia (INN), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari 09042, Italy.
- 50 Department of Chronic Disease Prevention, National Institute for Health and Welfare, FI-00271 Helsinki, Finland.
- 51 Department of Health Sciences, University of Leicester, Leicester LE1 6TP, UK.
- 52 Clinical Research Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21225, USA.
- 53 Medstar Research Institute, Baltimore, Maryland 21218, USA.
- 54 Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK.
- 55 Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK.
- 56 Department of Psychiatry, EMGO Institute, Neuroscience Campus Amsterdam, VU University Medical Center, 1007 MB Amsterdam, The Netherlands.
- 57 Division of Cardiology, Department of Medicine, Helsinki University Central Hospital (HUCH), FI-00029 Helsinki, Finland.
- 58 Unita Operativa Geriatria, Istituto Nazionale Ricovero e Cura Anziani (INRCA), Istituto Ricovero e Cura a Carattere Scientifico (IRCCS), Via Cassia 1167, 00189 Rome, Italy.
- 59 Hammersmith Hospital, National Heart and Lung Institute, Imperial College London, London W12 0NN, UK.
- 60 Gerontology Research Center, National Institute on Aging, 5600 Nathan Shock Drive, Baltimore, Maryland 21224, USA.
- 61 Department of Health Research and Policy, Stanford University, Stanford, California 94305, USA.
- 62 Department of Clinical Chemistry, University of Oulu, FI-90220 Oulu, Finland.
- 63 The John & Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa, Ottawa K1Y 4W7, Canada.
- 64 Departments of Medicine, Epidemiology, and Health Services, University of Washington, Group Health Research Institute, Group Health Cooperative, Seattle, Washington 98101, USA.
- 65 Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso 1, 39100 Bolzano, Italy – affiliated institute of the University of Lübeck, Germany.
- 66 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-17177 Stockholm, Sweden.
- 67 Amgen, Thousand Oaks, California 91320, USA.
- 68 Genetic and Molecular Epidemiology Laboratory, McMaster University, Hamilton, Ontario L8N3Z5, Canada.
- 69 Department of Clinical Genetics, Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands.
- 70 Institut für Humangenetik, Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, 85764 Neuherberg, Germany.
- 71 Institute of Human Genetics, Klinikum rechts der Isar, Technische Universität München, 81675 München, Germany.
- 72 Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK.
- 73 Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK.
- 74 Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford OX3 7LJ, UK.
- 75 Avon Longitudinal Study of Parents and Children, University of Bristol, Bristol BS8 2BN, UK.
- 76 Institute of Applied Genomics, via Linussio 51, 33100 Udine, Italy.
- 77 Cardiovascular Epidemiology and Genetics, Institut Municipal d'Investigació Mèdica, 08003 Barcelona, Spain.
- 78 Transplantation Laboratory, Haartman Institute, University of Helsinki, FI-00014 Helsinki, Finland.
- 79 Montreal Heart Institute (Research Center), Université de Montréal, Montréal, Québec H1T 1C8, Canada.
- 80 Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA.
- 81 Science Center, Tampere University Hospital, FI-33521 Tampere, Finland.
- 82 Institute of Regional Health Research and the Danish Twin Registry, Institute of Public Health, University of Southern Denmark, J.B.Winslows Vej 9B, DK-5000, Odense, Denmark.
- 83 Faculty of Medicine, Department of Public Health, University of Helsinki, FI-00014 Helsinki, Finland.
- 84 Massachusetts General Hospital Weight Center, Boston, Massachusetts 02114, USA.
- 85 Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, SE-75185 Uppsala, Sweden.
- 86 Department of Epidemiology & Biostatistics, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK.
- 87 Department of Public Health Science and General Practice, University of Oulu, FI-90220 Oulu, Finland.
- 88 Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, 93053 Regensburg, Germany.
- 89 Department of Epidemiology and Preventive Medicine Regensburg University Medical Center Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany.
- 90 Department of Biomedical Engineering and Computational Science, Aalto University School of Science and Technology, FI-00076 Aalto, Finland.
- 91 LIGHT Research Institute, Faculty of Medicine and Health, University of Leeds, Leeds LS2 9JT, UK.
- 92 Department of Medicine, Helsinki University Hospital, FI-00029 Helsinki, Finland.
- 93 Department of Psychiatry, Center for Neurobehavioral Genetics, The Jane and Terry Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA.
- 94 Clinical Research Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21225, USA.
- 95 Medizinische Klinik II, Universität zu Lübeck, 23538 Lübeck, Germany.
- 96 MRC-HPA Centre for Environment and Health, Imperial College London, London W2 1PG, UK.
- 97 BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK.
- 98 Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, SE-17177 Stockholm, Sweden.
- 99 National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, 20892, USA.
- 100 Departments of Vascular Medicine & Cardiology, Academic Medical Centre, 1105 AZ Amsterdam, The Netherlands.
- 101 Department of Physiology and Biophysics, University of Southern California, Los Angeles, California 90033, USA.
- 102 Geriatric Unit, Azienda Sanitaria Firenze (ASF), 50125 Florence, Italy.
- 103 Department of Medicine, Baylor College of Medicine, Houston, Texas 77030, USA.
- 104 Department of Medicine, Stanford University School of Medicine, Stanford, California 94305, USA.
- 105 Singapore Eye Research Institute, National University of Singapore, Singapore 168751, Republic of Singapore.
- 106 Departments of Medicine/Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Republic of Singapore.
- 107 Office of Population Studies Foundation, University of San Carlos, Cebu City 6000, Philippines.
- 108 Department of Anthropology, Northwestern University, Evanston, Illinois 60208, USA.
- 109 Department of Nutrition, Carolina Population Center, University of North Carolina, Chapel Hill, North Carolina 27516, USA.
- 110 Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi 39216, USA.
- 111 Children's Hospital Oakland Research Institute, Oakland, California 94609, USA.
- 112 Department of Cardiovascular Epidemiology and Population Genetics, Centro Nacional de Investigaciones Cardiovasculares, 28029 Madrid, Spain.
- 113 Nutrition and Genomics Laboratory, Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111, USA.
- 114 Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK.

115 Sage Bionetworks, Seattle, Washington 98109, USA.

116 Division of Community Health Sciences, St George's University of London, London SW17 0RE, UK.

117 Department of Cardiovascular Sciences, University of Leicester, NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester LE3 9QP, UK.

Author Contributions

Conceived and designed the experiments: Z Dastani, JB Richards, DM Waterworth, VE Mooser, C van Duijn, A Isaacs, JB Meigs, JC Florez, M-F Hivert, F Kronenberg, IM Heid, PP Pramstaller, JR Kizer, DS Siscovick, BM Psaty, O Raitakari, T Lehtimäki, JG Eriksson, M Perola, V Salomaa, RJF Loos, NJ Wareham, T Harris, L Qi, FB Hu, I Meulenbelt, M Kloppenburg, CM Ballantyne, H-E Wichmann, B Paulweber, L Kendenko, JG Wilson, A Bidulescu, S Musani, SG Buxbaum, S Redline, MA Allison, KL Mohlke, AP Morris, K Small. Performed the experiments: L Ferrucci, JM Egan, OD Carlson, P Vollenweider, C Lamina, NJ Wareham, J Chambers, J Kooner, R Frants, K Willems-vanDijk, SM Willems, TM Frayling, S Böhringer, F Kronenberg, AA Hicks, BM Psaty, I Chen, RP Tracy, M Kähönen, J Viikari, K Kristiansson, M-L Nuotio, K Lohman, A Kanaya, PE Slagboom, M Beekman, D van Heemst, I Meulenbelt, M Kloppenburg, CM Ballantyne, N Klopp, S Coassin, E Katsareli, A Bidulescu, MA Allison, LJ Rasmussen-Torvik, X Guo, JB

Borja, LS Adair, M Haun. Analyzed the data: Z Dastani, N Timpson, T Tanaka, KA Kapur, R Semple, X Yuan, P Henneman, A Isaacs, J Dupuis, J Grimsby, AK Manning, CT Liu, JRB Perry, AR Wood, F Kronenberg, IM Heid, TW Winkler, C Langenberg, C Fuchsberger, J Brody, L-P Lyytikäinen, RA Scott, Y Liu, M Garcia, L Qi, FB Hu, M Beekman, I Meulenbelt, H-W Uh, JS Pankow, S Kanoni, A Bidulescu, SG Buxbaum, Y Wu, AP Morris, K Small, TM Teslovich, BA Oostra, AR Wood. Contributed reagents/materials/analysis tools: DM Evans, B St. Pourcain, N Sattar, CMT Greenwood, TD Spector, M Ladoceur, CV Dedoussis, JB Meigs, F Kronenberg, IM Heid, TW Winkler, C Langenberg, AA Hicks, PP Pramstaller, BM Psaty, I Chen, RP Tracy, A Julia, B-M Loo, PE Slagboom, S Bandinelli, I Meulenbelt, H-W Uh, M Kloppenburg, DJ Couper, H-E Wichmann, B Paulweber, GV Dedoussis, P Deloukas, S Redline, T Johnson, BA Oostra, GD Smith. Wrote the paper: Z Dastani, JB Richards, CMT Greenwood, N Timpson, DM Waterworth, VE Mooser, CV Dedoussis, A Isaacs, JB Meigs, JC Florez, J Dupuis, JRB Perry, M-F Hivert, F Kronenberg, IM Heid, T Lehtimäki, M Perola, RA Scott, C Langenberg, RJF Loos, T Harris, DJ Couper, CM Ballantyne, BB Duncan, H-E Wichmann, KL Mohlke, AP Morris, K Small, R Semple. Undertook meta-analysis: Z Dastani, J Dupuis. Did multi-ethnic analysis: AP Morris. Did expression analysis: K Small. Wrote the first draft of the manuscript: Z Dastani.

References

- Hivert MF, Sullivan LM, Fox CS, Nathan DM, D'Agostino RB, Sr, et al. (2008) Associations of adiponectin, resistin, and tumor necrosis factor- α with insulin resistance. *J Clin Endocrinol Metab* 93: 3165–3172.
- Tilg H, Moschen AR (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 6: 772–783.
- Pischon T, Girman CJ, Hotamisliligil GS, Rifai N, Hu FB, et al. (2004) Plasma Adiponectin Levels and Risk of Myocardial Infarction in Men. *JAMA: The Journal of the American Medical Association* 291: 1730–1737.
- Li S, Shin HJ, Ding EL, van Dam RM (2009) Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 302: 179–188.
- Stumvoll M, Goldstein BJ, van Haefen TW (2005) Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 365: 1333–1346.
- Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, et al. (2006) Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *J Biol Chem* 281: 2654–2660.
- Wang Y, Zhou M, Lam KS, Xu A (2009) Protective roles of adiponectin in obesity-related fatty liver diseases: mechanisms and therapeutic implications. *Arq Bras Endocrinol Metabol* 53: 201–212.
- Comuzzie AG, Funahashi T, Sonnenberg G, Martin LJ, Jacob HJ, et al. (2001) The genetic basis of plasma variation in adiponectin, a global endophenotype for obesity and the metabolic syndrome. *Journal of Clinical Endocrinology and Metabolism* 86: 4321–4325.
- Vasseur F, Helbecq N, Dina C, Lobbens S, Delannoy V, et al. (2002) Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet* 11: 2607–2614.
- Cesari M, Narkiewicz K, De Toni R, Aldighieri E, Williams CJ, et al. (2007) Heritability of plasma adiponectin levels and body mass index in twins. *J Clin Endocrinol Metab* 92: 3082–3088.
- Liu PH, Jiang YD, Chen WJ, Chang CC, Lee TC, et al. (2008) Genetic and environmental influences on adiponectin, leptin, and BMI among adolescents in Taiwan: a multivariate twin/sibling analysis. *Twin Res Hum Genet* 11: 495–504.
- Menzaghi C, Trischitta V, Doria A (2007) Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. *Diabetes* 56: 1198–1209.
- Hivert MF, Manning AK, McAteer JB, Florez JC, Dupuis J, et al. (2008) Common variants in the adiponectin gene (ADIPOQ) associated with plasma adiponectin levels, type 2 diabetes, and diabetes-related quantitative traits: the Framingham Offspring Study. *Diabetes* 57: 3353–3359.
- Ling H, Waterworth DM, Stirradd HA, Pollin TI, Barter PJ, et al. (2009) Genome-wide Linkage and Association Analyses to Identify Genes Influencing Adiponectin Levels: The GEMS Study. *Obesity (Silver Spring)*.
- Heid IM, Henneman P, Hicks A, Coassin S, Winkler T, et al. (2010) Clear detection of ADIPOQ locus as the major gene for plasma adiponectin: results of genome-wide association analyses including 4659 European individuals. *Atherosclerosis* 208: 412–420.
- Richards JB, Waterworth D, O'Rahilly S, Hivert MF, Loos RJ, et al. (2009) A genome-wide association study reveals variants in ARL15 that influence adiponectin levels. *PLoS Genet* 5: e1000768. doi:10.1371/journal.pgen.1000768.
- Jee SH, Sull JW, Lee JE, Shin C, Park J, et al. (2010) Adiponectin concentrations: a genome-wide association study. *Am J Hum Genet* 87: 545–552.
- Wu Y, Li Y, Lange EM, Croteau-Chonka DC, Kuzawa CW, et al. (2010) Genome-wide association study for adiponectin levels in Filipino women identifies CDH13 and a novel uncommon haplotype at KNG1-ADIPOQ. *Hum Mol Genet* 19: 4955–4964.
- Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, et al. (2010) Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 42: 579–589.
- Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, et al. (2010) New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 42: 105–116.
- Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, et al. (2009) Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. *PLoS Genet* 5: e1000508. doi:10.1371/journal.pgen.1000508.
- Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, et al. (2010) Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 466: 707–713.
- Kilpeläinen TO, Zillikens MC, Stančáková A, Finucane FM, Ried JS, et al. (2011) Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. *Nature Genetics* In press.
- Morris AP (2011) Transethnic meta-analysis of genomewide association studies. *Genetic epidemiology* 35: 809–822.
- Nica AC, Parts L, Glass D, Nisbet J, Barrett A, et al. (2011) The Architecture of Gene Regulatory Variation across Multiple Human Tissues: The MuTHER Study. *PLoS Genet* 7: e1002003. doi:10.1371/journal.pgen.1002003.
- Nyholt DR (2004) A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. *Am J Hum Genet* 74: 765–769.
- Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, et al. (2010) Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet* 42: 949–960.
- Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, et al. (2009) Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. *Nat Genet* 41: 1110–1115.
- Takeuchi F, Serizawa M, Yamamoto K, Fujisawa T, Nakashima E, et al. (2009) Confirmation of multiple risk loci and genetic impacts by a genome-wide association study of type 2 diabetes in the Japanese population. *Diabetes* 58: 1690–1699.
- Adachi H, Tsujimoto M (2002) FEEL-1, a novel scavenger receptor with in vitro bacteria-binding and angiogenesis-modulating activities. *J Biol Chem* 277: 34264–34270.
- Gray SL, Vidal-Puig AJ (2007) Adipose tissue expandability in the maintenance of metabolic homeostasis. *Nutr Rev* 65: S7–12.
- Eremina V, Baelde HJ, Quaggin SE (2007) Role of the VEGF-a signaling pathway in the glomerulus: evidence for crosstalk between components of the glomerular filtration barrier. *Nephron Physiol* 106: p32–37.
- Buraczynska M, Ksiazek P, Baranowicz-Gaszczyk I, Jozwiak L (2007) Association of the VEGF gene polymorphism with diabetic retinopathy in type 2 diabetes patients. *Nephrol Dial Transplant* 22: 827–832.

34. Hu Y, Sun CY, Huang J, Hong L, Zhang L, et al. (2007) Antimyeloma effects of resveratrol through inhibition of angiogenesis. *Chin Med J (Engl)* 120: 1672–1677.
35. Szkudelski T, Szkudelska K (2011) Anti-diabetic effects of resveratrol. *Ann N Y Acad Sci* 1215: 34–39.
36. Ahn J, Lee H, Kim S, Ha T (2007) Resveratrol inhibits TNF-alpha-induced changes of adipokines in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 364: 972–977.
37. Kang L, Heng W, Yuan A, Baolin L, Fang H (2010) Resveratrol modulates adipokine expression and improves insulin sensitivity in adipocytes: Relative to inhibition of inflammatory responses. *Biochimie* 92: 789–796.
38. Kiss-Toth E, Bagstaff SM, Sung HY, Jozsa V, Dempsey C, et al. (2004) Human tribbles, a protein family controlling mitogen-activated protein kinase cascades. *J Biol Chem* 279: 42703–42708.
39. Sung HY, Guan H, Czibula A, King AR, Eder K, et al. (2007) Human tribbles-1 controls proliferation and chemotaxis of smooth muscle cells via MAPK signaling pathways. *J Biol Chem* 282: 18379–18387.
40. Waterworth DM, Ricketts SL, Song K, Chen L, Zhao JH, et al. (2010) Genetic variants influencing circulating lipid levels and risk of coronary artery disease. *Arterioscler Thromb Vasc Biol* 30: 2264–2276.
41. Park MH, Kim N, Lee JY, Park HY (2011) Genetic loci associated with lipid concentrations and cardiovascular risk factors in the Korean population. *J Med Genet* 48: 10–15.
42. Chasman DI, Pare G, Mora S, Hopewell JC, Peloso G, et al. (2009) Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis. *PLoS Genet* 5: e1000730. doi:10.1371/journal.pgen.1000730.
43. Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, et al. (2008) Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nat Genet* 40: 161–169.
44. Ivanov D, Philippova M, Antropova J, Gubaeva F, Iljinskaya O, et al. (2001) Expression of cell adhesion molecule T-cadherin in the human vasculature. *Histochemistry and cell biology* 115: 231–242.
45. Wise A, Foord SM, Fraser NJ, Barnes AA, Elshourbagy N, et al. (2003) Molecular identification of high and low affinity receptors for nicotinic acid. *J Biol Chem* 278: 9869–9874.
46. Westphal S, Borucki K, Taneva E, Makarova R, Luley C (2006) Adipokines and treatment with niacin. *Metabolism* 55: 1283–1285.
47. Plaisance EP, Lukasova M, Offermanns S, Zhang Y, Cao G, et al. (2009) Niacin stimulates adiponectin secretion through the GPR109A receptor. *Am J Physiol Endocrinol Metab* 296: E549–558.
48. Edmondson AC, Braund PS, Stylianou IM, Khara AV, Nelson CP, et al. (2011) Dense Genotyping of Candidate Gene Loci Identifies Variants Associated with High-Density Lipoprotein Cholesterol. *Circ Cardiovasc Genet*.
49. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, et al. (2001) Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86: 1930–1935.
50. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, et al. (2002) Adiponectin and development of type 2 diabetes in the Pima Indian population. *The Lancet* 360: 57–58.
51. Keating BJ, Tischfield S, Murray SS, Bhangale T, Price TS, et al. (2008) Concept, design and implementation of a cardiovascular gene-centric 50 k SNP array for large-scale genomic association studies. *PLoS ONE* 3: e3583. doi:10.1371/journal.pone.0003583.
52. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, et al. (2006) Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 38: 904–909.
53. Magi R, Morris AP (2010) GWAMA: software for genome-wide association meta-analysis. *BMC Bioinformatics* 11: 288.
54. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. *Brmj* 327: 557–560.
55. Theodoraki EV, Nikopentis T, Suhorutsenko J, Peppes V, Fili P, et al. (2010) Fibrinogen beta variants confer protection against coronary artery disease in a Greek case-control study. *BMC Med Genet* 11: 28.
56. Storey JD, Tibshirani R (2003) Statistical significance for genomewide studies. *Proc Natl Acad Sci U S A* 100: 9440–9445.